CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-235

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing Memorandum

NDA:	**21-235**	**Sponsor:**	**Eli Lilly and Company**
IND:			
Brand Name:	Prozac	**Priority Classification:**	Standard
Generic Name:	Fluoxetine	**Indication(s):**	Depression, OCD, bulimia
Drug Class:	Antidepressant	**Date of Submission:**	3 March, 2000
Dosage Form:	Capsule (Enteric coated delayed-release pellets)	**Route of Admin.:**	Oral
Dosing Regimen:	90 mg once-a-week	**Due Date of Review:**	September, 2000
Division:	DPE-1	**Medical Division:**	Neuropharm
Reviewer:	Vanitha Sekar	**Team Leader:**	Raman Baweja

Items included in NDA (CTD)	*Yes*	*No*	*Request*
Table of Contents present and sufficient to locate reports, tables, data, etc.	X		
Tabular Listing of All Human Studies	X		
HPK Summary	X		
Labeling	X		
Reference Bioanalytical and Analytical Methods	X		
Bioavailability and Bioequivalence Studies	X		
Mass Balance Study		X	
BA Studies		X	
Absolute BA		X	
Relative BA		X	
BE Studies	X		
Average BE	X		
Population BE		X	
Individual BE		X	
Food-Drug Interaction	X		
Dissolution Tests (In Vitro-In Vivo Comparison Studies)	X		
Studies Using Human Biomaterials		X	
Plasma Protein Binding Studies		X	
Blood/Plasma Ratio		X	
Metabolism Studies Using Hepatocytes, Microsomes,etc		X	
In Vitro Drug Interaction Studies		X	
Human Pharmacokinetics Studies			
PK, and Initial Safety and Tolerability in Healthy Volunteers	X		
Single Dose	X		
Multiple Dose	X		
PK, and Initial Safety and Tolerability in Patient Volunteers	X		
Single Dose		X	

Multiple Dose	X		
Dose Proportionality		X	
Single Dose		X	
Multiple Dose		X	
PK in Population Subsets to Evaluate Effects of Intrinsic Factors		X	
Ethnicity		X	
Gender		X	
Pediatrics		X	
Geriatrics		X	
Renal Impairment		X	
Hepatic Impairment		X	
PK to Evaluate Effects of Extrinsic Factors		X	
Drug-Drug Interaction: Effects on Primary Drug		X	
Drug-Drug Interaction: Effects of Primary Drug		X	
Population PK studies	X		
Summary Table of PK/PD Studies		X	
PK/PD studies in Volunteers		X	
PK/PD studies in patients		X	
Individual Datasets for all PK and PK/PD studies in electronic format		X	
Other		X	
Genotype/Phenotype Studies		X	
Chronopharmacokinetics		X	

This application is fileable.

QBR questions: (Key Issues to be Considered)

1. Do the studies provide adequate pharmacokinetic information for the 90 mg once weekly dose of fluoxetine?
2. Are the pharmacokinetic parameters of fluoxetine similar for the proposed 90 mg once weekly regimen and the current 20 mg/day regimen ?
3. Is the proposed fluoxetine enteric coated delayed-release capsule bioequivalent to the current immediate-release capsule ?

Requests/Comments are not to be sent to firm.

Signature [151] 4/25/00
Vanitha Sekar
Primary Reviewer

[151]
Raman Baweja 4/26/00
Secondary Reviewer

CC: NDA 21-235, HFD-850(Lee), HFD-860(Baweja, Mehta), CDER (Biopharm)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 21-235	**REVIEWER:** Vanitha J. Sekar, Ph.D
DRUG: Fluoxetine (Prozac ————	**APPLICANT:** Eli Lilly
FORMULATION(S): 90 mg enteric coated capsule	

TABLE OF CONTENTS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 21-235
PRIMARY REVIEWER: Vanitha J. Sekar, PhD
APPLICANT: Eli Lilly
DATE OF REVIEW: 10/10/00

DRUG: Prozac ——— (Fluoxetine HCl)
FORMULATION: Enteric coated Pellet Capsule
STRENGTH: 90 mg

INTRODUCTION AND BACKGROUND

The clinical pharmacology of fluoxetine and its active metabolite, norfluoxetine has been characterized in a number of studies and the important findings have been incorporated in the product's labeling (NDA # 18-936). This review does not contain information from the previous studies, but focuses on the review of the pharmacokinetic and bioavailability information for a new enteric coated formulation (a ——— formulation that contains enteric coated pellets of 90 mg fluoxetine given once weekly).

This review contains pharmacokinetic information from four clinical studies. Two of these are in healthy volunteers, one was a clinical efficacy and safety study in depressed patients and one was an adherence trial in depressed patients. In all these studies, fluoxetine and norfluoxetine were measured using validated bioanalytical methods.

INDICATION, DOSAGE AND ADMINISTRATION

Prozac ——— (90 mg once weekly) ———

CHEMISTRY

D.2.2. Composition and Dosage Form

Table D.2. Unit Formula

Ingredient	Quantity (mg/capsule)	Function	Reference to Standards
Active Ingredient			
Fluoxetine hydrochloride (equivalent to base)	[ ]		USP
Other Ingredients[1]			
Sucrose			NF
Hydroxypropyl Methylcellulose 5 cps			USP
Sugar Spheres			NF
Hydroxypropyl Methylcellulose	[ ]		USP
Sucrose			NF
Talc			USP
			ACS Reagent Grade
			JPE
Talc[3]	[ ]	[ ]	USP
Triethyl Citrate			NF

(continued)

Table D.2. Unit Formula (Concluded)

Ingredient	Quantity (mg/capsule)	Function	Reference to Standards
Color Coating			
Color Mixture White	[redacted]	[redacted]	
Hydroxypropyl Methylcellulose			USP
Talc[4]			USP
Total (calculated fill weight)			
Capsule Shell Size 0			
Opaque Green 412 Cap and Clear			
FD&C Blue No. 2[5]			
Titanium Dioxide			USP
D&C Yellow No. 10			
Gelatin			
Sodium Lauryl Sulfate			NF
Gelatin			NF
Imprinted with Black Ink			
[redacted]			

[4] FD&C Blue No. 2

Abbreviations: ACS = American Chemical Society, JPE = Japanese Pharmaceutical Excipients, NF = National Formulary, USP = United States Pharmacopeia.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

Has the applicant developed an adequate dissolution method and specifications?

The applicant's proposed dissolution method and specifications are as follows:

Dosage Form:	Enteric-coated Pellet Capsule Formulation
Strength:	90 mg
Apparatus Type:	USP Apparatus 3
Media:	0.1N HCl for 2 hours followed by pH 6.8 buffer
Volume:	250 mL
Proposed Dissolution Specification:	—, (Q) dissolved in — min

Based on the individual dissolution data for the batches used in the pivotal BE study, a dissolution specification of Q= — in 45 minutes may be recommended.

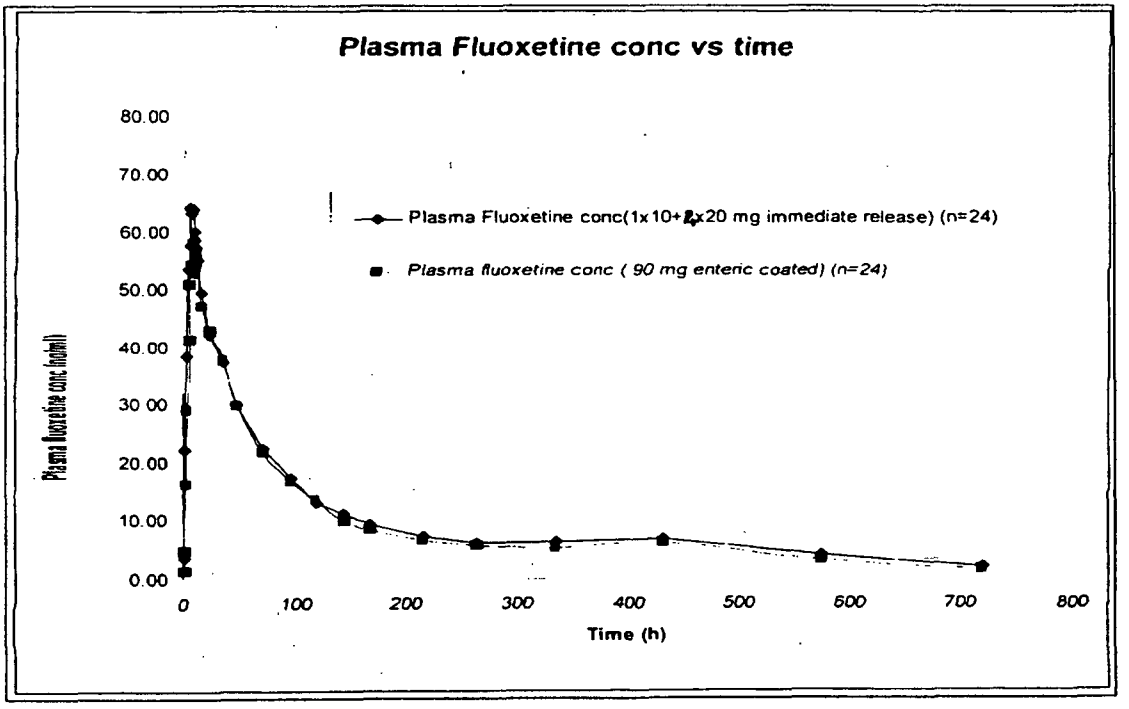
Is the new ——— release formulation of fluoxetine HCl bioequivalent to the current immediate release formulation?

The enteric coated pellet formulation is bioequivalent to the immediate release marketed formulation of fluoxetine.

Tmax for the enteric coated formulation is delayed by approximately 2 hours compared to that for the immediate release formulation. This may be due to delayed dissolution of the enteric coated tablet until it passes out of the stomach. This delay in Tmax is probably not clinically significant.

Bioequivalence assessments for Fluoxetine HCl (enteric coated vs. immediate release)

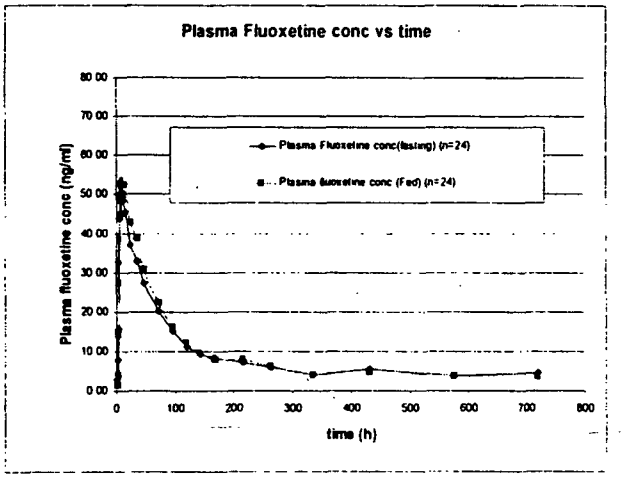
Parameter	Geom. Mean Ratio	90% confidence Interval	Result
LnCmax	0.89	0.84 to 0.94	Pass
lnAUC	0.95	0.89 to 1.01	Pass



The release formulation of fluoxetine HCl is bioequivalent to the current immediate release formulation.

Bioequivalence assessments for Fluoxetine (fed vs. fasted)

Parameter	Geom. Mean Ratio	90% confidence Interval	Result
LnCmax	1.05	0.97 to 1.13	Pass
lnAUC	1.11	1.06 to 1.16	Pass



Food does not affect the rate and extent of fluoxetine absorption following administration of the enteric coated pellet formulation.

Has the applicant compared the steady-state pharmacokinetic characteristics of the Once-Daily Regimen to the Once-Weekly Regimen?

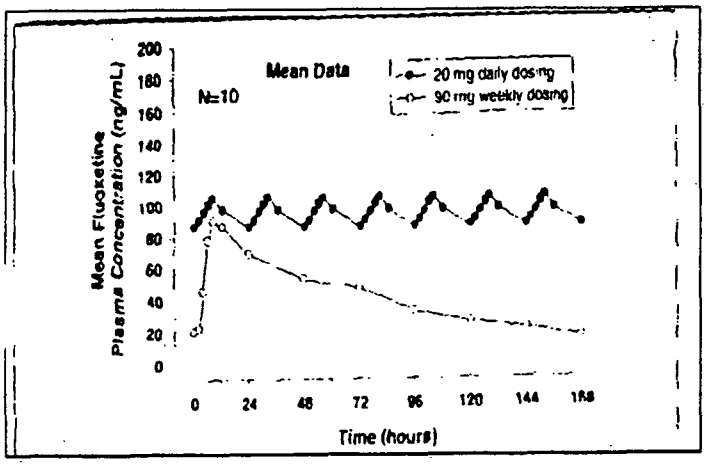
Average steady state fluoxetine concentrations were approximately 50% lower following the once-weekly regimen compared to the once-daily regimen.

The difference in average steady-state norfluoxetine concentrations between the 2 regimens was less pronounced.

Fluctuation between peak and trough concentrations were increased from daily to weekly dosing. (for fluoxetine: 24% (daily) to 164% (weekly) and for norfluoxetine: 17% (daily) to 43% (weekly))

Comparison of once-daily and once-weekly dosing showed that peak fluoxetine concentrations were similar for both regimens at steady-state.

Fluoxetine and norfluoxetine steady state concentrations were maintained for the 7 days following the once-weekly treatment.



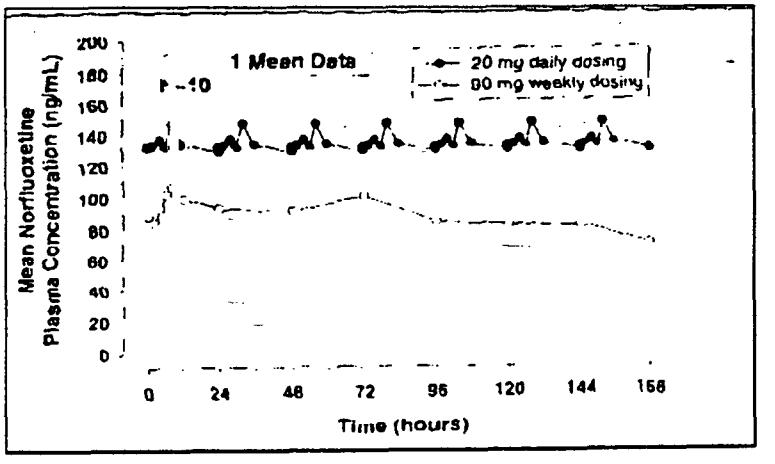


Table HCJO.11.2. Mean (range) of Pharmacokinetic Values for Steady-State Fluoxetine and Norfluoxetine Concentration Parameters After Giving Fluoxetine at a Dose of 20 mg Once Daily or 90 mg Once Weekly (N=19 Subjects)

Study HCJO	Fluoxetine Concentrations			Norfluoxetine Concentrations		
Pharmacokinetic Parameter (N=19 Subjects)	20 mg Once Daily Mean (range)	90 mg Once Weekly Mean (range)	90 mg weekly as a Percent of 20 mg Daily	20 mg Once Daily Mean (range)	90 mg Once Weekly Mean (range)	90 mg weekly as a Percent of 20 mg Daily
Cp^{ss}_{max} (ng/mL) Maximum Steady-State	127 (52 to 238)	103 (53 to 194)	81%	132 (60 to 227)	92 (37 to 188)	70%
$\overline{Cp}^{ss}$ (ng/mL) Average Steady-State	114 (46 to 217)	53 (21 to 118)	46%	121 (56 to 214)	75 (32 to 138)	62%
Cp^{ss}_{min} (ng/mL) Minimum Steady-State	100 (38 to 206)	24 (4.4 to 75)	24%	112 (51 to 203)	59 (21 to 108)	53%
F^{max}_{min} (%) Fluctuation	24 (11 to 36)	164 (91 to 236)	---	17 (10 to 27)	43 (29 to 62)	---
$AUC_{0\text{-}168}$ (ng•hr/mL) 7 day Area Under the Curve	19080 * (7800 to 36490) *	8830 (3490 to 19740)	46%	20400 * (9420 to 35980) *	12600 (5380 to 23120)	62%

* $AUC_{0\text{-}24}$ multiplied times 7.

The applicant has adequately characterized the pharmacokinetic characteristics of the new enteric coated formulation of fluoxetine HCl

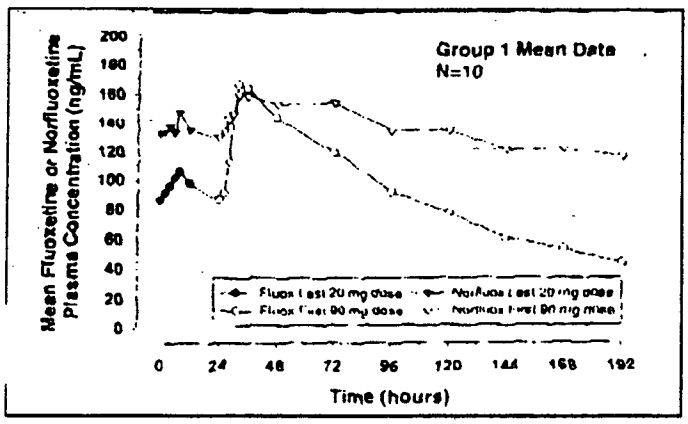
Has the applicant adequately assessed the period of transition between the once-daily regimen and the once-weekly regimen?

The applicant has compared the transition from once-daily fluoxetine to once–weekly fluoxetine using 2 scenarios:

- First dose of once weekly capsule from the day following the last daily dose of fluoxetine (Group 1)
- First dose of once weekly capsule 7 days after the last daily dose of fluoxetine (Group 2)

Cmax for fluoxetine following the first 90 mg dose was approximately 1.7 fold higher than the Cmax value for the established 20 mg once daily regimen for Group 1. This difference was not seen for Group 2.

There was a transient increase in the average steady-state concentrations of fluoxetine observed following immediate transition to the once-weekly regimen



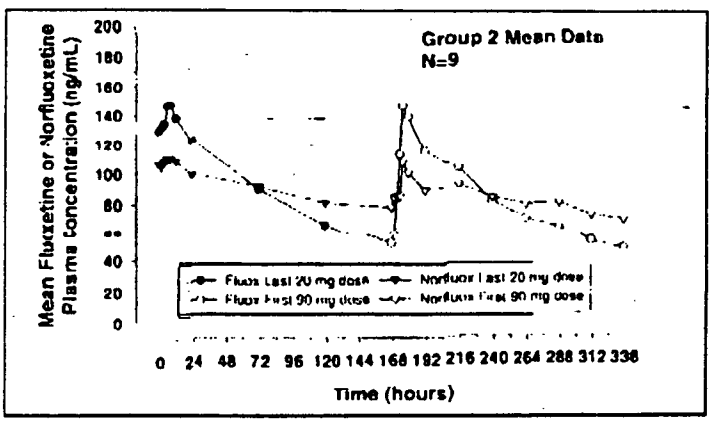


Table HCJO.11.3. Mean Pharmacokinetic Values for the Transition Phase from Once Daily to Once Weekly Dosing For Group 1 (Immediate Transition After the Last Fluoxetine Dose of 20 mg Daily) and Group 2 (7 Days After the Last Fluoxetine Dose of 20 mg Daily)

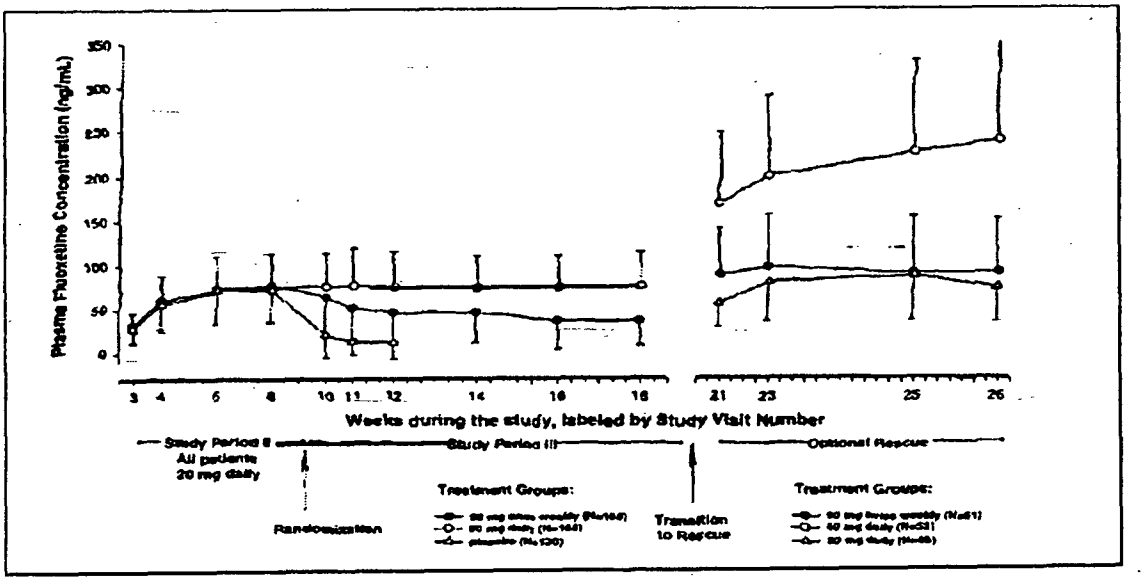
Study HCJO	Group 1 (N=10)			Group 2 (N=9)		
Pharmacokinetic Parameter	Last 20 mg Once Daily Mean	First 90 mg Once Weekly Mean	90 mg weekly as a Percent of 20 mg Daily	Last 20 mg Once Daily Mean	First 90 mg Once Weekly Mean	90 mg weekly as a Percent of 20 mg Daily
Fluoxetine C_{max} (ng/mL)	105 (52 to 181)	169 (100 to 271)	161%	151 (101 to 238)	150 (97 to 255)	99%
Norfluoxetine C_{max} (ng/mL)	148 (65 to 227)	168 (64 to 257)	114%	115 (60 to 219)	107 (54 to 218)	93%
Fluoxetine AUC (ng-hr/mL)	15910 [a] (7800 to 27750) [a]	10130 [b] (5969 to 14690) [b]	64%	22610 [a] (14280 to 36490) [a]	12700 [b] (6423 to 25510) [b]	56%
Norfluoxetine AUC (ng-hr/mL)	22670 [a] (9950 to 35980) [a]	15750 [b] (3190 to 25300) [b]	69%	17880 [a] (9420 to 34580)	10240 [b] (4727 to 14980) [b]	57%

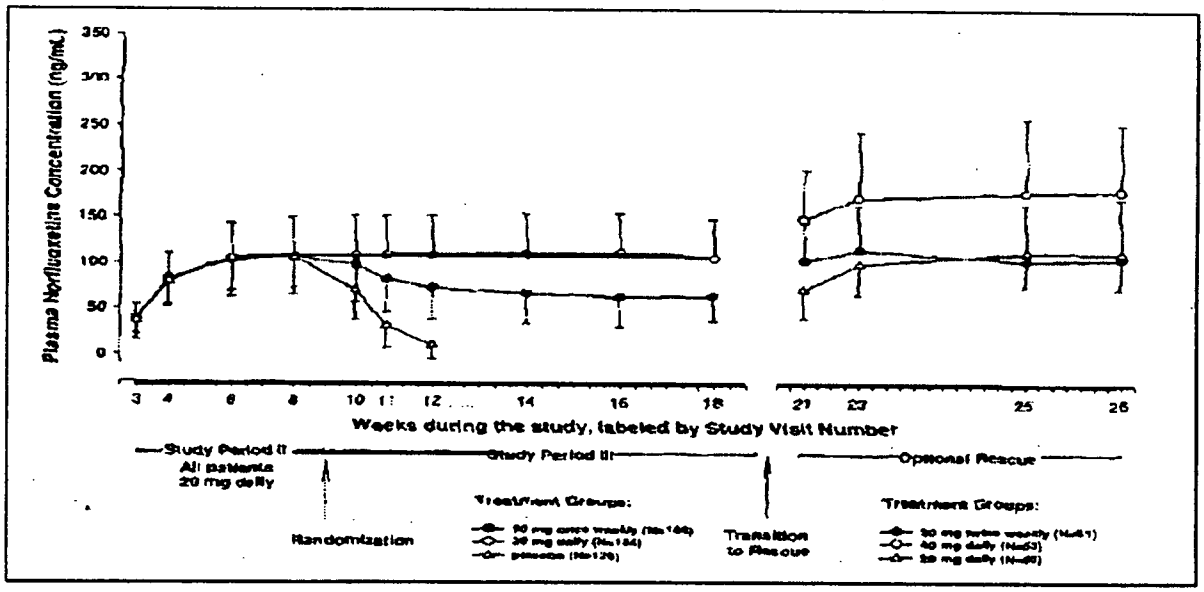
From a strictly pharmacokinetic perspective, it may be better to separate the first 90 mg once weekly dose and the last 20 mg once daily dose by one week. Clinically the once weekly treatment may be initiated any time within 7 days of the last 20 mg daily dose. However, the label will reflect the pharmacokinetic findings.

Has the applicant characterized the steady state pharmacokinetics of the new formulation in the target patient population?

Mean steady state plasma fluoxetine and norfluoxetine concentrations in depressed patients who received 90 mg once weekly were approximately 60% of the mean concentrations achieved following a dose of 20 mg once daily.

Mean steady state fluoxetine /norfluoxetine concentrations following 90 mg once weekly were similar in depressed patients in this study and in healthy volunteers. (Fluoxetine: healthy (53 ng/ml) versus patients (43 ng/m)l; Norfluoxetine: healthy (75 ng/ml) versus healthy (69 ng/ml)).





Has the applicant assessed the ability of depressed patients to comply with the prescribed regimen of once-daily or once-weekly dosing?

The compliance rate (based on plasma fluoxetine and norfluoxetine concentrations) was 79% for patients randomized to the 90 mg once weekly regimen and 84% for patients randomized to the 20 mg once daily treatment. These differences are not significant.

RECOMMENDATION: The clinical pharmacology/biopharmaceutics information provided in NDA 21-235 is adequate to support approval of Prozac ___ for the treatment of major depression.

Comments to Applicant: Based on the individual dissolution data for the batches used in the pivotal BE study, we recommend a dissolution specification of Q= ___ in 45 minutes.

Labeling Comments: Please see attachment.

151 11/27/00

Vanitha J. Sekar, Ph.D.
Reviewer, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

[151] 11/3/2000

Concurrence: Emmanuel Fadiran, Ph.D.
Acting Team Leader, Neuropharmacological Drug Section, DPE I
Office of Clinical Pharmacology and Biopharmaceutics

cc: HFD-120 NDA 21-235
/MO/ K. Smith
/CSO/P. David
/Biopharm/V. Sekar
/Acting TL Biopharm/E. Fadiran
HFD-860 /DD DPE1/M. Mehta
HFD-860 /DPE I
CDR

Title of study: Single Dose Safety and Bioavailability Study: 90 mg Enteric Coated Bead Formulation versus 90 mg Fluoxetine Capsule and Effect of Food on the Absorption of Fluoxetine from the 90 mg Enteric Coated Bead Formulation (Study HCIX, Item 6, Volume 5)

Objectives: The objectives were to: 1) assess the safety and tolerability of single doses of an enteric-coated formulation in healthy males and females, 2) compare the bioavailability of a single 90 mg fluoxetine enteric coated pellet formulation to the marketed 10 and 20 mg fluoxetine capsules, and, 3) study the effect of food on the oral bioavailability of the 90 mg enteric coated formulation of fluoxetine.

Study Design and Methods: The study was an open label, randomized, single dose, 2-period crossover study conducted in two parts. In the first part, the bioavailability of a single 90 mg fluoxetine enteric coated pellet formulation was compared to the marketed 10 and 20 mg fluoxetine capsules in 24 subjects (8 males and 16 females). In the second part, the effect of food on the oral bioavailability of the 90 mg enteric coated formulation of fluoxetine was assessed in 24 subjects (8 males and 16 females). Since fluoxetine is metabolized by ——— all subjects were phenotyped (using the dextromethorphan challenge) for identifying poor and extensive metabolizers of fluoxetine.

Part 1/Group 1: Test: 1x90 mg fluoxetine enteric coated pellet capsule; Reference: 1x10 mg + 4x20 mg fluoxetine capsules. Washout period of at least 34 days.
Part 2/Group 2: Test: 1x90 mg enteric coated pellet capsule, fed; Reference: 1x90 mg enteric coated pellet capsule, fasted. Washout period of at least 34 days. The FDA-recommended high fat meal was used to assess the effect of food. The standardized meal consisted of 2 white bread slices, 10 g butter, 2 eggs, 2tsp oil, 2 strips of bacon, 4 oz of hash browns and 8 oz of whole milk.

Blood samples for fluoxetine and norfluoxetine were collected predose and at 1, 2, 3, 4, 5, 6,, 7, 8,, 9, 10, 11, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, 216, 264, 336, 432, 576, and 720 hours.

Plasma samples were analyzed for fluoxetine and norfluoxetine using ———— with mass spectrometry detection. The limit of quantification was ——— The method was linear in the range of ——— . The precision and accuracy information for the quality control samples and standard curve concentration during sample analysis for this study were acceptable (summary information not provided by applicant). Urine samples were analyzed for dextromethorphan and dextorphan using HPLC with ———— A ratio of 0.34 or greater classified a subject as a poor metabolizer (PM) and a ration of less than 0.34 classified a subject as an extensive metabolizer.

Pharmacokinetic parameters (Cmax, AUC, Tmax) were obtained using noncompartmental methods. To assess bioequivalence, analysis of variance (ANOVA) was performed on log transformed Cmax and AUC and 90% confidence intervals were calculated. Bioequivalence limits of ——— were applied.

Results:

Assessment of bioequivalence of the enteric coated pellet capsule formulation

Demographics: Subjects demographic data are shown below in Table1.

Table 1

Demographic Description for Subjects in Group 1

Subject Number	Smoking Habits	Gender	Age (yrs)	Height (in)	Weight (lb)	Frame	Race	Dextromethorphan/Dextrorphan (Ratio)
1	Non-Smoker	Female	22	70	160	Medium	Caucasian	0.008
2	Non-Smoker	Female	70	65	168	Large	Caucasian	0.007
3	Non-Smoker	Female	26	65	127	Small	Caucasian	0.004
4	Non-Smoker	Male	45	68	194	Large	Caucasian	0.004
5	Non-Smoker	Female	24	67	179	Large	Caucasian	0.019
6	Non-Smoker	Female	57	66	172	Large	Caucasian	0.012
7	Non-Smoker	Female	25	64	115	Medium	Hispanic	1.553 (PM)
8	10-14 Cigarettes A Day	Male	39	74	153	Medium	Caucasian	0.029
9	Non-Smoker	Female	26	62	122	Small	Caucasian	0.004
10	10-14 Cigarettes A Day	Male	61	73	219	Large	Caucasian	0.013
11	Non-Smoker	Male	25	74	180	Medium	Caucasian	0.010
12	Non-Smoker	Male	72	70	150	Medium	Caucasian	0.006
13	Non-Smoker	Female	23	69	149	Small	Caucasian	0.007
14	10-14 Cigarettes A Day	Female	38	66	148	Medium	Caucasian	0.003
15	1-2 Packs of Cigarettes A Day	Female	30	65	116	Small	Caucasian	0.014
16	10-14 Cigarettes A Day	Female	32	64	134	Large	Caucasian	0.008
17	1-2 Packs of Cigarettes A Day	Male	53	68	170	Medium	Caucasian	0.006
18	Non-Smoker	Female	40	68	176	Large	Caucasian	0.006
19	Non-Smoker	Male	65	71	206	Large	Caucasian	0.046
20	Non-Smoker	Female	23	66	135	Medium	Caucasian	0.005
21	15-19 Cigarettes A Day	Female	36	61	108	Small	Caucasian	0.009
22	Non-Smoker	Female	29	68	135	Large	Caucasian	1.437 (PM)
23	Non-Smoker	Female	29	61	118	Small	Asian	0.003
24	Non-Smoker	Male	21	73	166	Medium	Caucasian	0.003
Mean			38	67	154			
Min			21	61	108			
Max			72	74	219			
SD			16	4	30			

Pharmacokinetics:. Individual and mean fluoxetine pharmacokinetic parameters for Group 1 are shown below (see tables 2 and 3). Mean plasma concentration time profile for the enteric coated capsule (90 mg) and immediate release capsule (1x10 + 4x20 mg) is shown in Figure 1.

Table 2a

Pharmacokinetic Parameters For Fluoxetine, Treatment A: 90 mg Fluoxetine Standard Oral Capsules (1 x 10 mg + 4 x 20 mg)

Subject	Gender	C_{max} (ng/mL)	T_{max} (hr)	β (hr^{-1})	$t_{1/2}$ (hr)	AUC_{0-t} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)
1	F						
2	F						
3	F						
5	F						
6	F						
7	F						
9	F						
13	F						
14	F						
15	F						
16	F						
18	F						
20	F						
21	F						
22	F						
23	F						
4	M						
8	M						
10	M						
11	M						
12	M						
17	M						
19	M						
24	M						
Mean (n=24; all)		69.2	7.0	0.0144	62.2	5068.7	5246.2
SD		19.8	2.0	0.0064	37.9	3569.2	3691.8
%CV		28.6	27.9	44.7	60.8	70.4	70.4

Table 2b

Pharmacokinetic Parameters For Fluoxetine,
Treatment B: 90 mg Fluoxetine Enteric Coated Pellet Capsule (1 x 90 mg)

Subject	Gender	C_{max}	T_{max}	β	$t_{1/2}$	AUC_{0-t}	$AUC_{0-\infty}$
1	F						
2	F						
3	F						
5	F						
6	F						
7	F						
9	F						
13	F						
14	F						
15	F						
16	F						
18	F						
20	F						
21	F						
22	F						
23	F						
4	M						
8	M						
10	M						
11	M						
12	M						
17	M						
19	M						
24	M						
Mean (n=24; all)		62.0	8.9	0.0143	60.0	4767.9	4909.3
SD		19.5	1.8	0.0057	33.4	3205.1	3285.0
% CV		31.4	20.8	40.1	55.7	67.2	66.9

Table 3a

Pharmacokinetic Parameters For Norfluoxetine,
Treatment A: 90 mg Fluoxetine Standard Oral Capsules (1 x 10 mg + 4 x 20 mg)

Subject	Gender	C_{max} (ng/mL)	T_{max} (hr)	β (hr^{-1})	$t_{1/2}$ (hr)	AUC_{0-t} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)
1	F						
2	F						
3	F						
5	F						
6	F						
7	F						
9	F						
13	F						
14	F						
15	F						
16	F						
18	F						
20	F						
21	F						
22	F						
23	F						
4	M						
8	M						
10	M						
11	M						
12	M						
17	M						
19	M						
24	M						
Mean (n=24; all)		34.9	97.5	0.0040	214.1	12612.8	14807.6
SD		10.1	44.1	0.0016	118.6	3842.0	5790.9
% CV		29.0	45.2	45.1	55.4	30.5	39.1

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Table 3b

Pharmacokinetic Parameters For Norfluoxetine.
Treatment B: 90 mg Fluoxetine Enteric Coated Pellet Capsule (1 x 90 mg)

Subject	Gender	C_{max} (ng/mL)	T_{max} (hr)	β (hr^{-1})	$t_{1/2}$ (hr)	AUC_{0-t} (ng•hr/mL)	$AUC_{0-\infty}$ (ng•hr/mL)
1	F						
2	F						
3	F						
4	M						
5	F						
6	F						
7	F						
8	M						
9	F						
10	M						
11	M						
12	M						
13	F						
14	F						
15	F						
16	F						
17	M						
18	F						
19	M						
20	F						
21	F						
22	F						
23	F						
24	M						
Mean (n=2		32.8	117.6	0.0042	203.4	11840.0	13677.7
SD		9.3	73.0	0.0018	107.4	3518.3	5189.1
% CV		28.4	62.1	43.5	52.8	29.7	37.9

Figure 1a

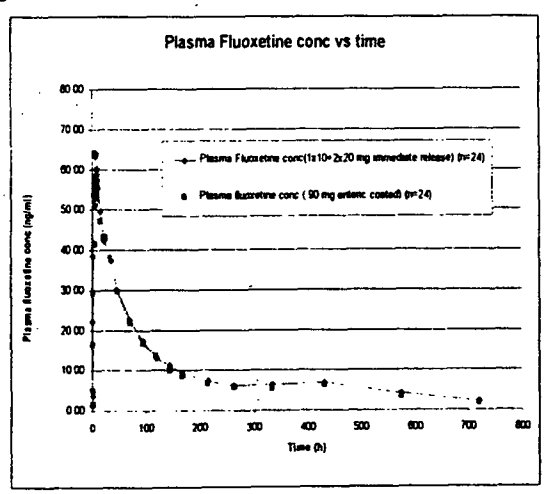
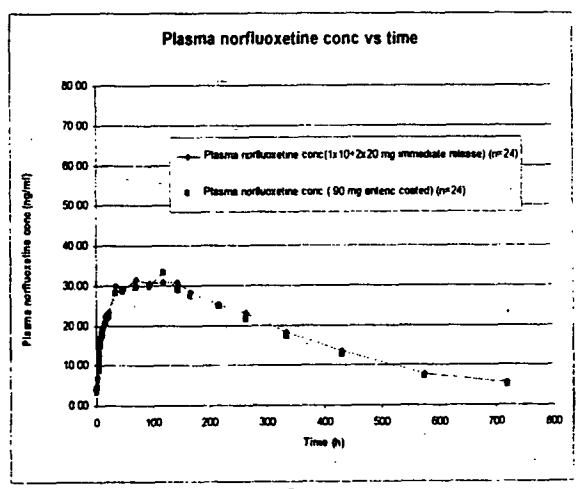


Figure 1b



Mean fluoxetine and norfluoxetine pharmacokinetic parameters for the 90 mg enteric coated pellet capsule and those following administration of the immediate release capsules (1x10+4x20 mg) are similar. Tmax for fluoxetine was delayed by approximately 1-2 hours following administration of the enteric coated pellet. The delayed Tmax for fluoxetine following the enteric coated capsule suggests that absorption of fluoxetine is delayed because dissolution is prevented until the dosage form leaves the stomach or until the gastrointestinal pH is greater than 5.5 (to prevent GI side effects).

Bioequivalence assessment comparing the enteric coated formulation to the marketed immediate release capsule based on log transformed Cmax and AUC values of fluoxetine and norfluoxetine are shown in Tables 5a and 5b. The results suggest that the enteric coated pellet capsule is bioequivalent to the immediate release capsule at a dose of 90 mg.

Table 4 a: Bioequivalence assessments for Fluoxetine (enteric coated vs. immediate release)

Parameter	Geom. Mean Ratio	90% confidence Interval	Result
LnCmax	0.89	0.84 to 0.94	Pass
lnAUC	0.95	0.89 to 1.01	Pass

Table 4 b: Bioequivalence assessments for Norfluoxetine(enteric coated vs. immediate release)

Parameter	Geom. Mean Ratio	90% confidence Interval	Result
LnCmax	0.94	0.90 to 0.98	Pass
lnAUC	0.93	0.89 to 0.97	Pass

Effect of food on the enteric coated pellet capsule formulation

Demographics: Subjects demographic data are shown below in Table 5

Table 5

Demographic Description for Subjects in Group 2

Subject Number	Smoking Habits	Gender	Age (yrs)	Height (in)	Weight (lb)	Frame	Race	Dextromethorphan/Dextrorphan (Ratio)
25	10-14 Cigarettes A Day	Female	52	65	176	Large	Caucasian	0.031
26	10-14 Cigarettes A Day	Female	27	62	152	Large	Caucasian	0.005
27	0-4 cigarettes A Day	Female	25	61	131	Medium	Caucasian	0.003
28	0-4 cigarettes A Day	Female	21	65	154	Medium	Caucasian	0.005
29	Non-Smoker	Female	52	69	192	Large	Caucasian	0.007
30	Non-Smoker	Male	22	69	162	Medium	Caucasian	0.095
31	Non-Smoker	Male	28	71	138	Small	Caucasian	0.003
32	Non-Smoker	Female	47	69	155	Medium	Caucasian	0.010
33	Non-Smoker	Female	51	63	130	Small	Caucasian	0.005
34	Non-Smoker	Female	51	65	129	Medium	Caucasian	0.014
35	Non-Smoker	Male	32	68	174	Large	Caucasian	0.003
36	Non-Smoker	Female	43	67	163	Large	Caucasian	0.011
37	Non-Smoker	Female	25	66	126	Medium	Caucasian	0.016
38	Non-Smoker	Female	43	66	170	Large	Caucasian	0.031
39	Non-Smoker	Female	58	64	135	Small	Caucasian	1.555 (PM)
40	Non-Smoker	Male	19	74	149	Small	Caucasian	0.007
41	Non-Smoker	Female	65	63	153	Medium	Caucasian	0.016
42	Non-Smoker	Female	61	65	122	Small	Caucasian	0.008
43	Non-Smoker	Male	22	76	238	Large	Caucasian	0.003
44	Non-Smoker	Male	51	71	192	Large	Caucasian	0.006
45	Non-Smoker	Male	22	68	142	Medium	Caucasian	0.009
46	0-4 cigarettes A Day	Male	23	75	227	Large	Caucasian	0.006
47	5-9 Cigarettes A Day	Female	19	66	156	Medium	Caucasian	0.003
48	Chews Tobacco	Female	19	66	132	Medium	Caucasian	0.003
Mean			37	67	158			
Min			19	61	122			
Max			65	76	238			
SD			16	4	30			

Pharmacokinetics:. Individual and mean fluoxetine pharmacokinetic parameters for Group 2 in the fed and fasted state are shown below (see tables 6 and 7). Mean plasma concentration time profiles for the enteric coated capsule (90 mg) in the fed and fasted state are shown in Figure 2.

Table 6a

Pharmacokinetic Parameters for Fluoxetine,
Treatment C: 90 mg Fluoxetine Enteric Coated Pellet Capsule Administered After 8 Hours Fasting

Subject	Gender	C_{max} (ng/mL)	T_{max} (hr)	β (hr^{-1})	$t_{1/2}$ (hr)	AUC_{0-t} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)
25	F						
27	F						
28	F						
29	F						
32	F						
33	F						
34	F						
36	F						
37	F						
38	F						
39	F						
41	F						
42	F						
47	F						
48	F						
30	M						
31	M						
35	M						
40	M						
43	M						
44	M						
45	M						
46	M						
Mean (n=24, all)		58.8	9.4	0.0160	54.7	4268.0	4422.5
SD		20.5	1.7	0.0063	35.2	3460.8	3656.5
%CV		34.9	18.2	39.5	64.3	81.1	82.7

Table 6b

Pharmacokinetic Parameters For Fluoxetine,
Treatment D: 90 mg Fluoxetine Enteric Coated Pellet Capsule Administered With Fo

Subject	Gender	C_{max} (ng/mL)	T_{max} (hr)	β (hr^{-1})	$t_{1/2}$ (hr)	AUC_{0-t} (ng·hr/mL)	$AUC_{0-\infty}$ (ng·hr/mL)
25	F						
27 a	F						
28	F						
29	F						
32	F						
33	F						
34	F						
36	F						
37	F						
38	F						
39	F						
41	F						
42	F						
47	F						
48	F						
30	M						
31	M						
35	M						
40	M						
43	M						
44	M						
45	M						
46	M						
Mean (n=24; all)		60.5	11.0	0.0154	57.0	4517.2	4680.3
SD		16.8	3.1	0.0065	34.3	3193.5	3350.7
%CV		27.8	28.1	42.4	60.1	70.7	71.6

Table 7a

Pharmacokinetic Parameters For Norfluoxetine,
Treatment C: 90 mg Fluoxetine Enteric Coated Pellet Capsule Administered After 8 Hours Fast

Subject	Gender	C_{max} (ng/mL)	T_{max} (hr)	β (hr^{-1})	$t_{1/2}$ (hr)	AUC_{0-t} (ng•hr/mL)	$AUC_{0-\infty}$ (ng•hr/mL)
25	F						
27	F						
28	F						
29	F						
32	F						
33	F						
34	F						
36	F						
37	F						
38	F						
39	F						
41	F						
42	F						
47	F						
48	F						
30	M						
31	M						
35	M						
40	M						
43	M						
44	M						
45	M						
46	M						
Mean (n=24; all)		37.1	97.7	0.0041	191.3	12144.2	13692.4
SD		10.1	39.5	0.0013	71.1	3308.3	4459.3
%CV		27.3	40.4	32.8	37.2	27.2	32.6

Table 7b

Pharmacokinetic Parameters For Norfluoxetine,
Treatment D: 90 mg Fluoxetine Enteric Coated Pellet Capsule Administered With Food

Subject	Gender	C_{max} (ng/mL)	T_{max} (hr)	β (hr^{-1})	$t_{1/2}$ (hr)	AUC_{0-t} (ng•hr/mL)	$AUC_{0-\infty}$ (ng•hr/mL)
25	F						
27a	F						
28	F						
29	F						
30	M						
31	M						
32	F						
33	F						
34	F						
35	M						
36	F						
37	F						
38	F						
39	F						
40	M						
41	F						
42	F						
43	M						
44	M						
45	M						
46	M						
47	F						
48	F						
Mean (n=2		38.3	121.8	0.0039	200.7	13009.3	14788.1
SD		9.5	84.2	0.0014	78.7	3007.6	4051.7
%CV		24.7	69.1	34.5	39.2	23.1	27.4

Figure 2a

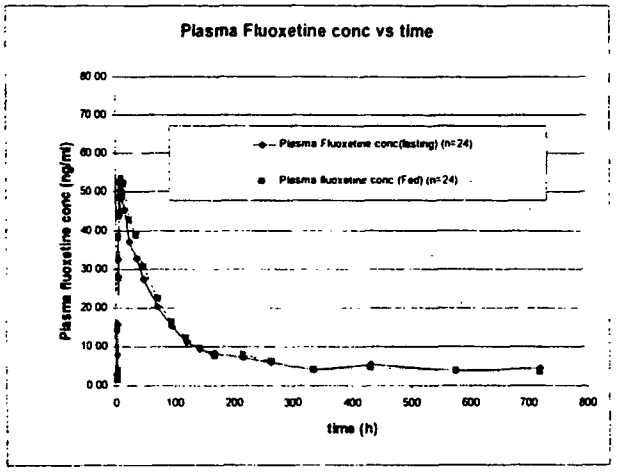
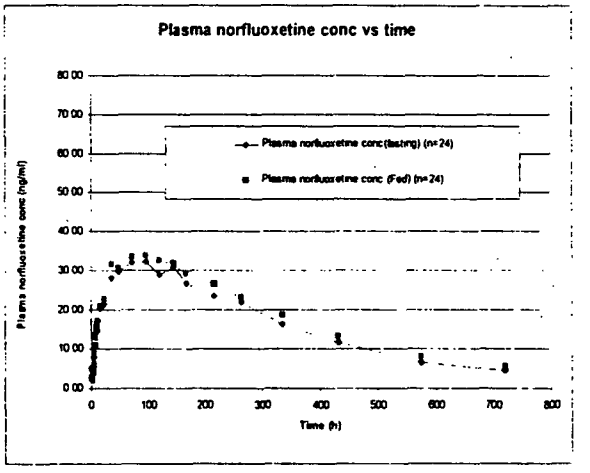


Figure 2b



Mean fluoxetine and norfluoxetine pharmacokinetic parameters for the 90 mg enteric coated pellet capsule in the fed and fasted states are similar. Tmax in the fed state was delayed by approximately 1-2 hours for fluoxetine and 24 hours for norfluoxetine compared to the fasted state following administration of the enteric coated pellet. Bioequivalence assessment to evaluate the effect of food on the enteric coated formulation based on log transformed Cmax and AUC values of fluoxetine and norfluoxetine are shown in Tables 8a and 8b. The results suggest that rate and extent of absorption of fluoxetine are similar in the fed and fasted state following administration of the enteric coated pellet capsule.

Table 4 a: Bioequivalence assessments for Fluoxetine (fed vs. fasted)

Parameter	Geom. Mean Ratio	90% confidence Interval	Result
LnCmax	1.05	0.97 to 1.13	Pass
lnAUC	1.11	1.06 to 1.16	Pass

Table 4 b: Bioequivalence assessments for Norfluoxetine (fed vs. fasted)

Parameter	Geom. Mean Ratio	90% confidence Interval	Result
LnCmax	1.05	0.99 to 1.10	Pass
lnAUC	1.10	1.05 to 1.15	Pass

Conclusions:

1. The enteric coated pellet formulation is bioequivalent to the immediate release marketed formulation of fluoxetine.
2. Tmax for the enteric coated formulation is delayed by approximately 2 hours compared to that for the immediate release formulation. This may be due to delayed dissolution of the enteric coated tablet until it passes out of the stomach.
3. Food does not affect the rate and extent of fluoxetine absorption following administration of the enteric coated pellet formulation, but causes a delay in Tmax of approximately 2 hours for fluoxetine and 24 hours for norfluoxetine.

Title of study: Multiple Dose, Fluoxetine Steady State Switch from Once Daily to Once Weekly Dosing (Study HCJO, Item 6, Volume 9)

Objectives: The objective was to characterize the plasma concentration profile and transition from steady state concentrations resulting from administration of 20 mg fluoxetine once daily to steady-state concentrations resulting from administration of 90 mg fluoxetine once weekly.

Study Design and Methods: The study was an open label, randomized, stratified (by gender) multiple dose study in healthy males and females to investigate the transition from steady state concentrations resulting from administration of 20 mg fluoxetine once daily to new steady-state concentrations resulting from administration of 90 mg fluoxetine once weekly.

The study consisted of 3 study periods: 1) 60 mg fluoxetine once daily for 7 days as a loading dose (days 1-7), 2) 20 mg fluoxetine once daily for 14 days (Days 8-21) , and 3) 90 mg fluoxetine (enteric coated) administered once weekly for 6 weeks. There were 2 groups of subjects in the study. Subjects in Group 1 (6 males, 7 females) and Group 2 (6 males, 6 females) received the same treatment for the first 2 study periods. For Period 3, subjects in Group 1 received the 90 mg enteric coated once weekly capsule from the day following the last daily dose of 20 mg fluoxetine (Day 22 onward). Subjects in Group 2 started receiving their first dose of 90 mg enteric coated once weekly capsule 7 days after the last daily dose of 20 mg fluoxetine (Day 28 onward). Since fluoxetine is metabolized by all subjects were phenotyped (using the dextromethorphan challenge) for identifying poor and extensive metabolizers of fluoxetine.

Blood samples for fluoxetine and norfluoxetine were collected at the following times:

Group 1: Days 1, 8, 10, 14, 18 and 20: predose and 12 hours after dosing
Days 19 and 21: predose and 2, 4, 6, 8 and 12 hours after dosing
Day 22: predose, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120 and 144 after dosing
Days 29, 36, 43, 50: predose and 12 hours after dosing
Day 57: predose, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 216, 288 and 360 after dosing (the additional samples after 144 hours were drawn to measure plasma concentrations that occur if weekly dosing was deferred up to 15 days after a dosing).

Group 2: Days 1, 8, 10, 14, 18 and 20: predose and 12 hours after dosing
Days 19 and 21: predose and 2, 4, 6, 8 and 12 hours after dosing
Days 22: 24, 72 and 120 hours after the last 20 mg daily dose administered on day 21
Day 28: predose, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120 and 144 after dosing
Days 35, 42, 49, 56: predose and 12 hours after dosing
Day 63: predose, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, after dosing

Plasma samples were analyzed for fluoxetine and norfluoxetine using a validated LC/MS/MS method. The limit f quantification was ———. The method was linear n the range of ——— The precision for QC samples (for fluoxetine) as expressed by %RSD ranged from ——— and accuracy for QC samples (for fluoxetine) as expressed by %RE ranged from ———. The precision for QC samples (for norfluoxetine) as expressed by %RSD ranged from ——— and accuracy for QC samples (for norfluoxetine) as expressed by %RE ranged from ———.

Urine samples were analyzed for dextromethorphan and dextorphan using HPLC with———
——— A ratio of 0.34 or greater classified a subject as a poor metabolizer (PM) and a ration of less than 0.34 classified a subject as an extensive metabolizer.

Pharmacokinetic parameters were obtained using noncompartmental methods. The main steady state pharmacokinetic parameters to define fluoxetine pharmacokinetic characteristics in this study were: Average steady state concentrations (Cpss), minimum steady state concentrations (Cpminss), maximum steady state concentrations (Cpmaxss), fluctuation in steady state concentrations (Fminmax), steady state area under the curve (AUC0-t).

Results:

Demographics: Subjects demographic data are shown below in Table1.

Table 1

Subject	Group	Gender	Age yr	Height in	Weight lbs	Weight kg	Frame	Origin	
1	1	Male	48	69	145	65.8	Medium	Caucasian	EM
3	1	Male	55	72	213	96.6	Large	Caucasian	EM
4	1	Male	69	68	132	59.9	Small	Caucasian	EM
7	1	Male	23	70	178	80.7	Medium	Black	EM
9	1	Male	37	71	197	89.4	Large	Black	EM
10	1	Male	22	68	187	84.8	Large	Caucasian	EM
101	1	Female	45	59	133	60.3	Medium	Caucasian	EM
104	1	Female	53	65	166	75.3	Large	Caucasian	EM
106	1	Female	46	65	157	71.2	Medium	Caucasian	EM
107	1	Female	27	65	137	62.1	Small	Caucasian	EM
108	1	Female	36	65	138	62.6	Medium	Caucasian	EM
111	1	Female	24	65	113	51.3	Small	Caucasian	EM
113	1	Female	19	63	113	51.3	Small	Caucasian	EM
2	2	Male	21	69	155	70.3	Medium	Caucasian	PM
5	2	Male	40	67.5	166	75.3	Medium	Black	EM
6	2	Male	25	68	190	86.2	Large	Caucasian	EM
8	2	Male	27	69	203	92.1	Large	Hispanic	EM
11	2	Male	22	68	138	62.6	Medium	Caucasian	EM
12	2	Male	72	70	197	89.4	Large	Caucasian	PM
102	2	Female	42	68	115	52.2	Small	Caucasian	EM
103	2	Female	26	64	117	53.1	Small	Caucasian	EM
105	2	Female	29	64	156	70.8	Large	Caucasian	EM
109	2	Female	32	66	174	78.9	Large	Caucasian	EM
110	2	Female	59	67	126	57.2	Medium	Caucasian	EM
112	2	Female	22	64	144	65.3	Small	Caucasian	PM

Pharmacokinetics: 19 of the 25 subjects completed all aspects of the study. Of these, 10 were in Group1 and 9 were in Group 2. The major design difference between Groups 1 and 2 was the interval of time between the last 20 mg daily dose and the first weekly dose. Subjects in Group 1 received the 90 mg enteric coated once weekly tablet from the day following the last daily dose of 20 mg fluoxetine. Subjects in Group 2 started receiving their first dose of 90 mg enteric coated once weekly tablet 7 days after the last daily dose of 20 mg fluoxetine.

The mean overall observed plasma fluoxetine and norfluoxetine plasma concentrations for Groups 1 and 2 are shown in Figure 1.

Figure 1

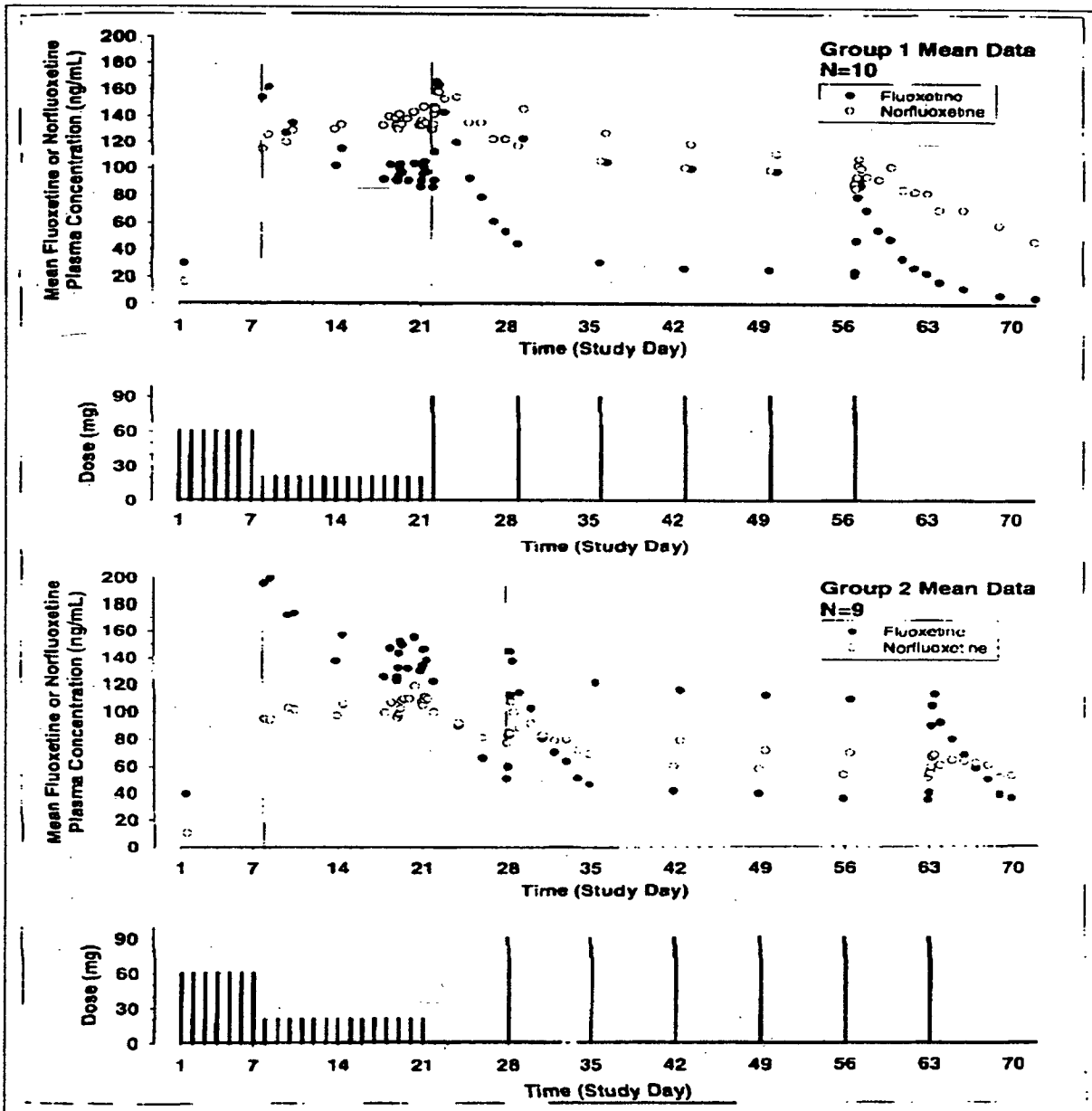


Figure HCJO.11.5. Mean observed fluoxetine and norfluoxetine plasma concentrations and fluoxetine dose administration over time for Group 1 and Group 2.

The loading dose of 60 mg once daily fluoxetine for 7 days results in concentrations that are higher than steady state concentrations expected following administration of 20 mg once daily fluoxetine. However, this loading dose was necessary to achieve norfluoxetine concentrations in the range that would be expected following administration of 20 mg once daily fluoxetine. Following the loading dose, administration of 20 mg once daily fluoxetine results in expected steady-state concentrations of fluoxetine and norfluoxetine. When the first weekly dose is given the very next daily following the last daily dose (Group 1), fluoxetine

concentrations are transiently higher. This transient increase in fluoxetine concentrations is not seen when the weekly dose is given one week following last daily dose of fluoxetine (Group 2). This difference was also observed for norfluoxetine, though it was not as pronounced. From a pharmacokinetic perspective, it may be better to wait 7 days following the last daily dose of fluoxetine to start the weekly dose of fluoxetine. Administration of the 90 mg weekly dose resulted in lower average steady-state fluoxetine and norfluoxetine concentrations. The fluctuation in the steady state fluoxetine concentrations was larger for the once-weekly dosing than for the once-daily dosing.

Inspection of the overall plasma concentration-time profiles in Figure 1 suggests that mean norfluoxetine concentrations are higher in Group 1 compared to Group 2. This is probably because Group 2 included 3 subjects who were classified as poor metabolizers. Poor metabolizers have lower norfluoxetine concentrations and higher fluoxetine concentrations than extensive metabolizers.

Comparison of steady-state fluoxetine and norfluoxetine concentrations for once-weekly versus once-daily dosing: Mean steady-state fluoxetine and norfluoxetine concentrations for these 2 regimens are compared in Figures 2-5. Peak fluoxetine concentrations were similar for both regimens art steady-state. Average steady state fluoxetine concentrations were approximately 50% lower following the once-weekly regimen compared to the once-daily regimen (figures 2 and 3). The difference in average steady-state norfluoxetine concentrations between the 2 regimens was less pronounced (figures 4 and 5). It should be noted that fluoxetine and norfluoxetine steady state concentrations were maintained for the 7 days following the once-weekly treatment. Fluoxetine and norfluoxetine concentrations were (approximately 50% and 40%, respectively) following the once-weekly regimen compared to the once-daily regimen (Table 2).

Figure 2

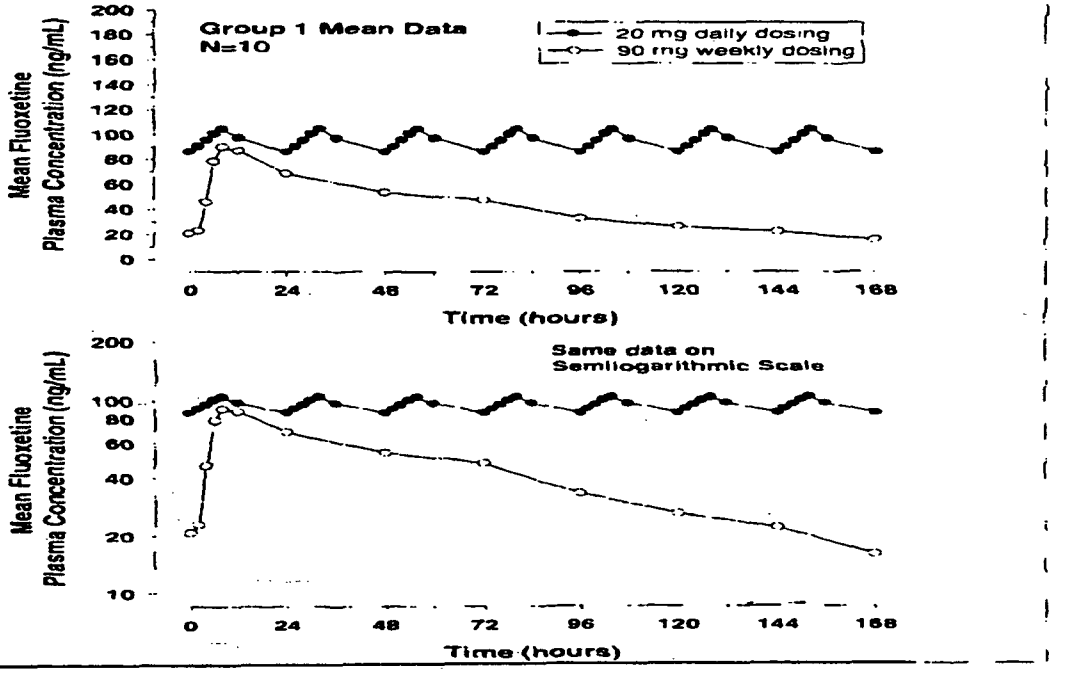


Figure HCJO.11.6. Mean fluoxetine plasma concentrations following 20 mg fluoxetine once-daily dosing (data from Day 21 replicated) and 90 mg fluoxetine once-weekly dosing (data from Days 57 to 64) for Group 1.

Figure 3

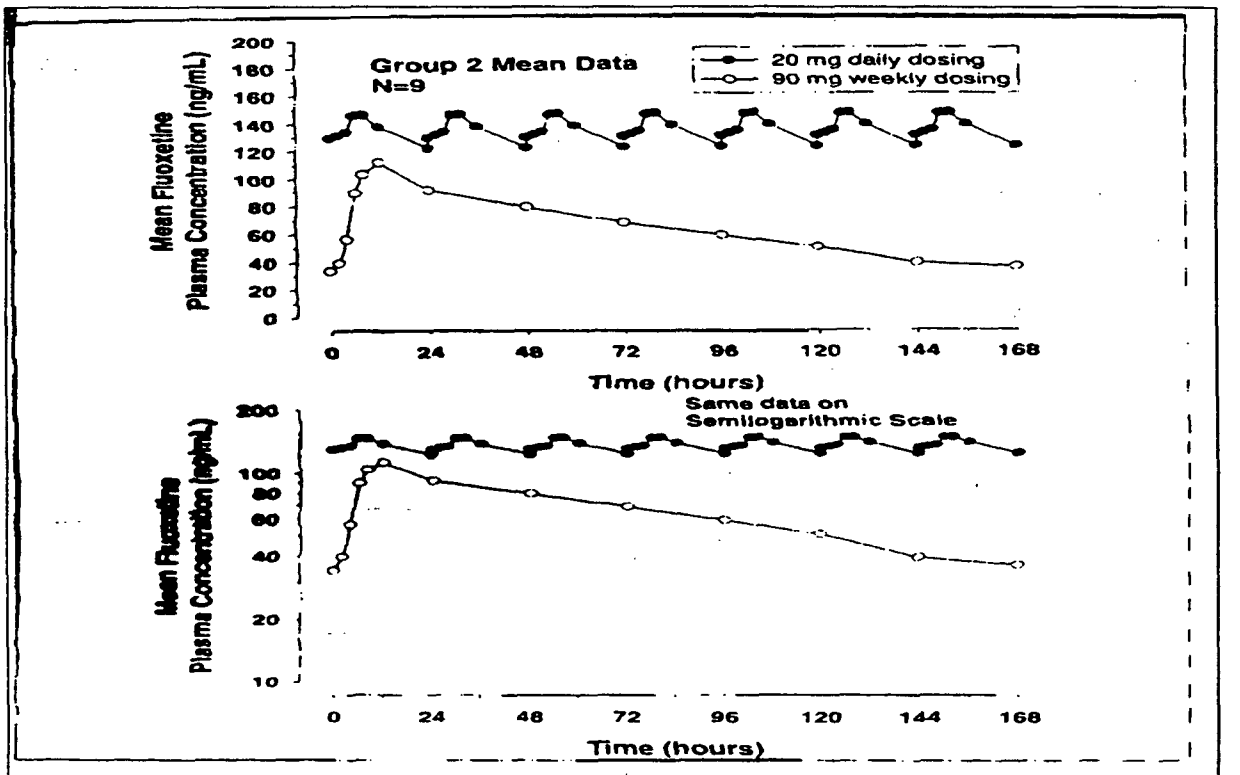


Figure HCJO.11.7. Mean fluoxetine plasma concentrations following 20 mg fluoxetine once-daily dosing (data from Day 21 replicated) and 90 mg fluoxetine once-weekly dosing (data from Days 63 to 70) for Group 2.

Figure 4

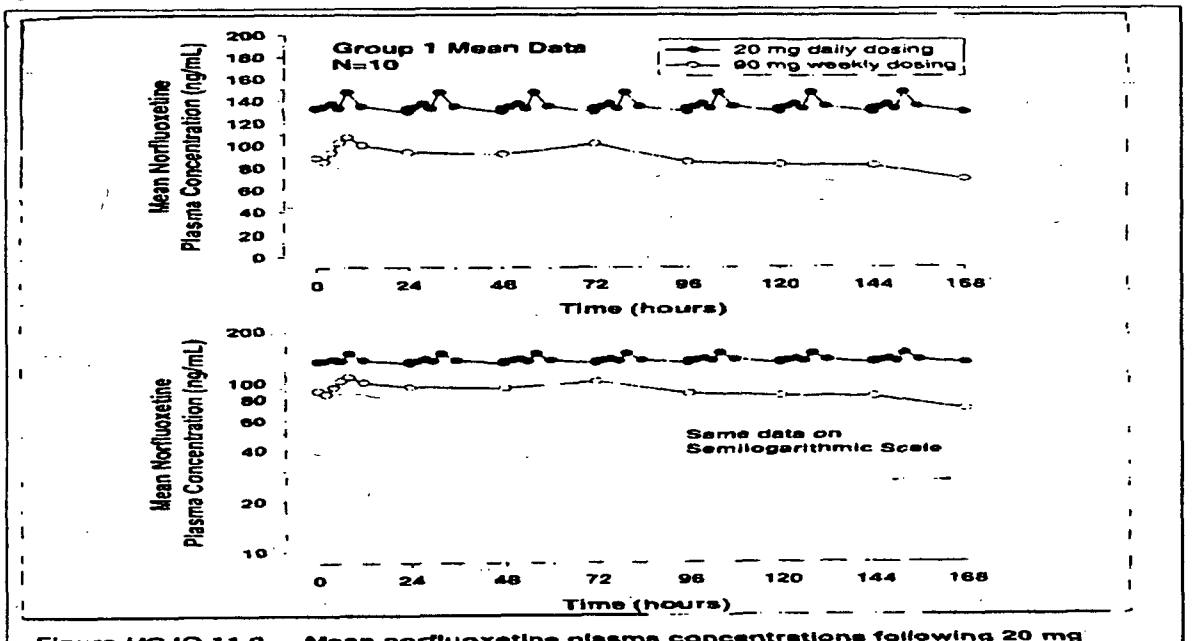


Figure HCJO.11.9. Mean norfluoxetine plasma concentrations following 20 mg fluoxetine once-daily dosing (data from Day 21 replicated) and 90 mg fluoxetine once-weekly dosing (data from Days 57 to 64) for Group 1.

Figure 5

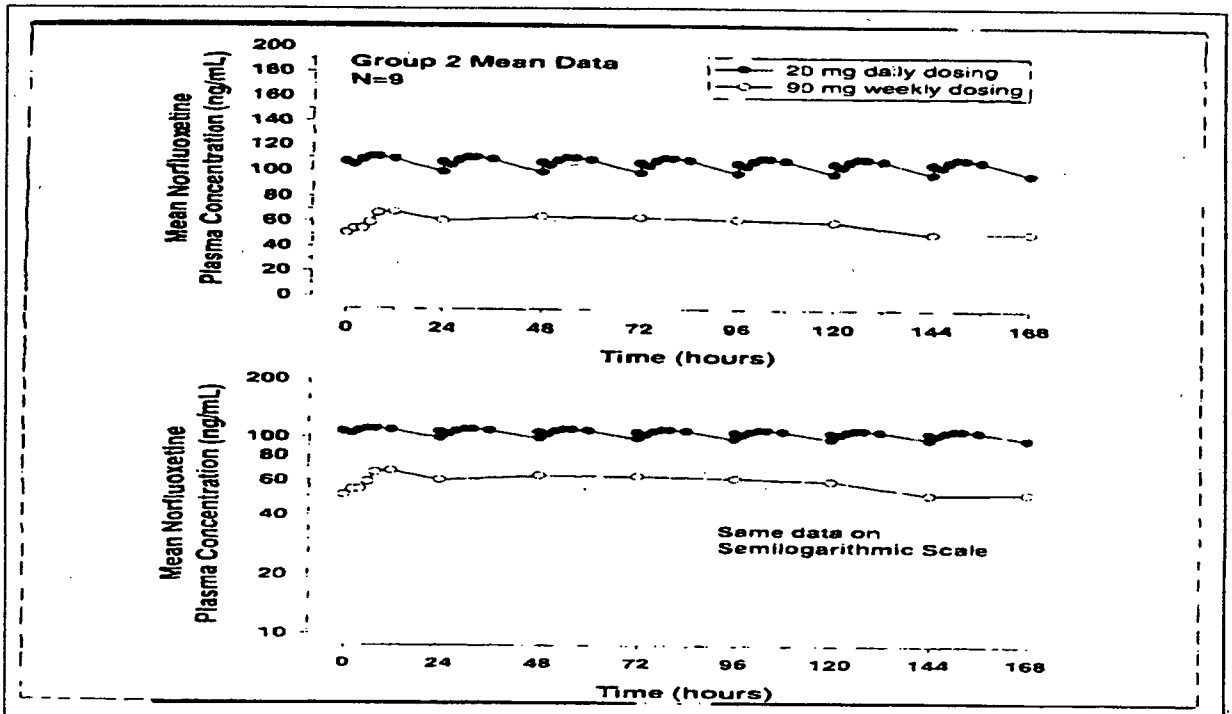


Figure HCJO.11.10. **Mean norfluoxetine plasma concentrations following 20 mg fluoxetine once-daily dosing (data from Day 21 replicated) and 90 mg fluoxetine once-weekly dosing (data from Days 63 to 70) for Group 2.**

Mean (Range) steady state pharmacokinetic parameters following the 20 mg once daily dose and the 90 mg once weekly dose for fluoxetine and norfluoxetine are shown in Table 2.

Table 2

Table HCJO.11.2. Mean (range) of Pharmacokinetic Values for Steady-State Fluoxetine and Norfluoxetine Concentration Parameters After Giving Fluoxetine at a Dose of 20 mg Once Daily or 90 mg Once Weekly (N=19 Subjects)

Study HCJO	Fluoxetine Concentrations			Norfluoxetine Concentrations		
Pharmacokinetic Parameter (N=19 Subjects)	20 mg Once Daily Mean (range)	90 mg Once Weekly Mean (range)	90 mg weekly as a Percent of 20 mg Daily	20 mg Once Daily Mean (range)	90 mg Once Weekly Mean (range)	90 mg weekly as a Percent of 20 mg Daily
Cp^{ss}_{max} (ng/mL) Maximum Steady-State	127 (52 to 238)	103 (53 to 194)	81%	132 (60 to 227)	92 (37 to 188)	70%
$\overline{Cp}^{ss}$ (ng/mL) Average Steady-State	114 (46 to 217)	53 (21 to 118)	46%	121 (56 to 214)	75 (32 to 138)	62%
Cp^{ss}_{min} (ng/mL) Minimum Steady-State	100 (38 to 206)	24 (4.4 to 75)	24%	112 (51 to 203)	59 (21 to 108)	53%
F^{max}_{min} (%) Fluctuation	24 (11 to 36)	164 (91 to 236)	---	17 (10 to 27)	43 (29 to 62)	---
$AUC_{0\text{-}168}$ (ng•hr/mL) 7 day Area Under the Curve	19080 * (7800 to 36490) *	8830 (3490 to 19740)	46%	20400 * (9420 to 35980) *	12600 (5380 to 23120)	62%

* $AUC_{0\text{-}24}$ multiplied times 7.

Steady state pharmacokinetic parameters for fluoxetine were lower following the once-weekly treatment compared to the once-daily regimen. This difference was less pronounced for norfluoxetine. There was a large inter-individual variability in the pharmacokinetic parameters for both, fluoxetine and norfluoxetine.

Comparison of transition from once-daily to once-weekly dosing: Mean steady-state concentrations for Group 1 and 2 are compared in Figures 6 and 7. These figures show the transition from 20 mg once daily to 90 mg once weekly dosing. These profiles suggest that the week long interval between the last daily 20 mg dose and the once-weekly 90 mg dose (Group 2) results in a smoother transition to the new once-weekly dosing regimen.

Figure 6

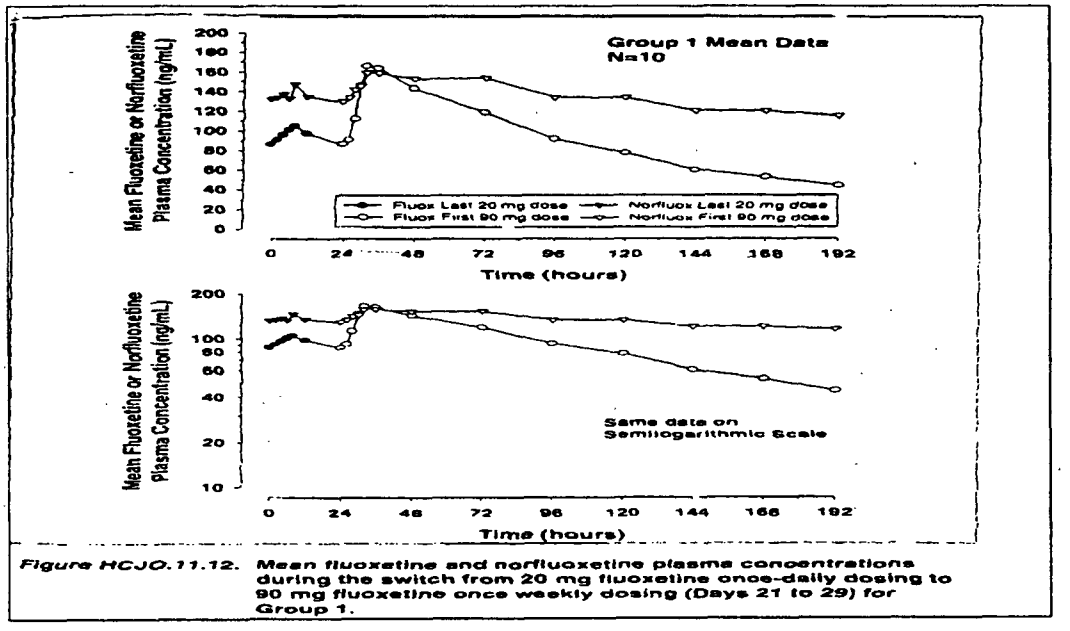


Figure HCJO.11.12. *Mean fluoxetine and norfluoxetine plasma concentrations during the switch from 20 mg fluoxetine once-daily dosing to 90 mg fluoxetine once weekly dosing (Days 21 to 29) for Group 1.*

Figure 7

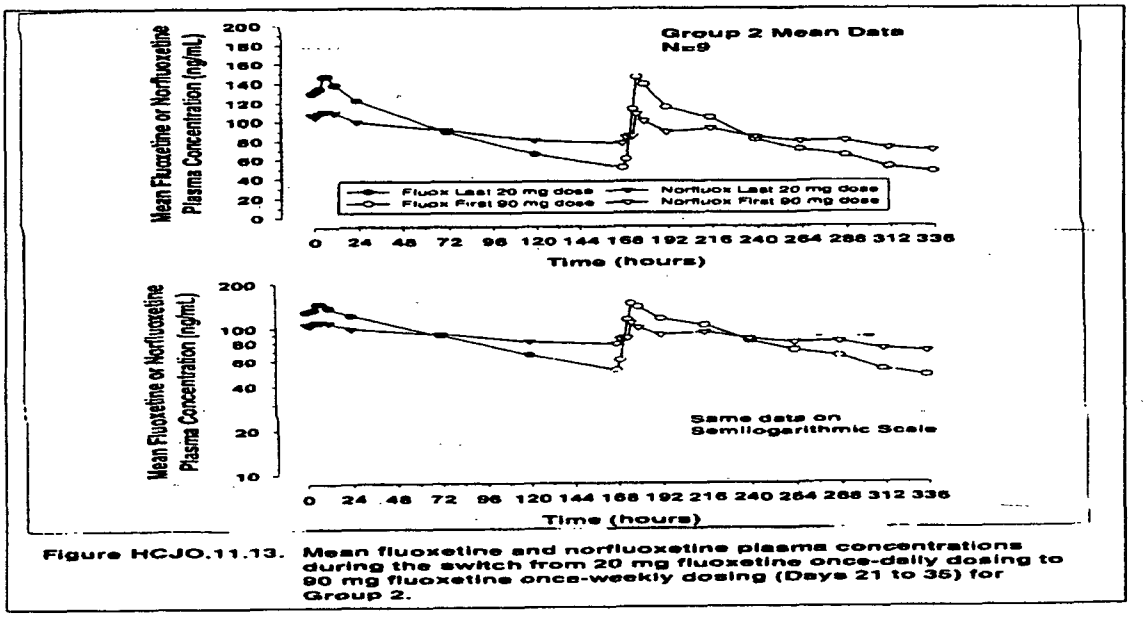


Figure HCJO.11.13. **Mean fluoxetine and norfluoxetine plasma concentrations during the switch from 20 mg fluoxetine once-daily dosing to 90 mg fluoxetine once-weekly dosing (Days 21 to 35) for Group 2.**

Mean (Range) steady state pharmacokinetic parameters for the transition phase from once-daily to once-weekly dosing for Group 1 (immediate transition) and Group 2 (Delayed transition) are shown in Table 3.

Table 3

Table HCJO.11.3. Mean Pharmacokinetic Values for the Transition Phase from Once Daily to Once Weekly Dosing For Group 1 (Immediate Transition After the Last Fluoxetine Dose of 20 mg Daily) and Group 2 (7 Days After the Last Fluoxetine Dose of 20 mg Daily)

Study HCJO	Group 1 (N=10)			Group 2 (N=9)		
Pharmacokinetic Parameter	Last 20 mg Once Daily Mean	First 90 mg Once Weekly Mean	90 mg weekly as a Percent of 20 mg Daily	Last 20 mg Once Daily Mean	First 90 mg Once Weekly Mean	90 mg weekly as a Percent of 20 mg Daily
Fluoxetine C_{max} (ng/mL)	105 (52 to 181)	169 (100 to 271)	161%	151 (101 to 238)	150 (97 to 255)	99%
Norfluoxetine C_{max} (ng/mL)	148 (65 to 227)	168 (64 to 257)	114%	115 (60 to 219)	107 (54 to 218)	93%
Fluoxetine AUC (ng•hr/mL)	15910 [a] (7800 to 27750) [a]	10130 [b] (5969 to 14690) [b]	64%	22610 [a] (14280 to 36490) [a]	12700 [b] (6423 to 25510) [b]	56%
Norfluoxetine AUC (ng•hr/mL)	22670 [a] (9950 to 35980) [a]	15750 [b] (3190 to 25300) [b]	69%	17880 [a] (9420 to 34580)	10240 [b] (4727 to 14980) [b]	57%

There was a large inter-individual variability in the pharmacokinetic parameters. The results show than Cmax for fluoxetine following the first 90 mg dose was approximately 1.7 fold higher than the Cmax value for the established 20 mg once daily regimen for Group 1. This difference was not seen for Group 2. This combined with the transient increase in the average steady-state concentrations of fluoxetine observed following immediate transition to the once-weekly regimen, suggests that from a pharmacokinetic perspective, it may be better to separate the first 90 mg once weekly dose and the last 20 mg once daily dose by one week.

Comparison of the plasma concentration-time profile following the first and last 90 mg fluoxetine dose: Plasma fluoxetine and norfluoxetine concentrations following the first and last 90 mg once-weekly fluoxetine for Groups 1 and 2 are shown in Figures 8-11. The profiles show that Group 2 had less of a difference between the first and last dose fluoxetine concentrations because of the 7 day interval before the first 90 mg once weekly dose and the last 20 mg once-daily dose. In contrast for Group 1, there were larger differences in fluoxetine concentrations between the first and last 90 mg once weekly dose caused by dosing the 90 mg dose the day after the last 20 mg once daily dose. This difference was also observed for norfluoxetine, however the magnitude of the difference was much smaller.

Figure 8

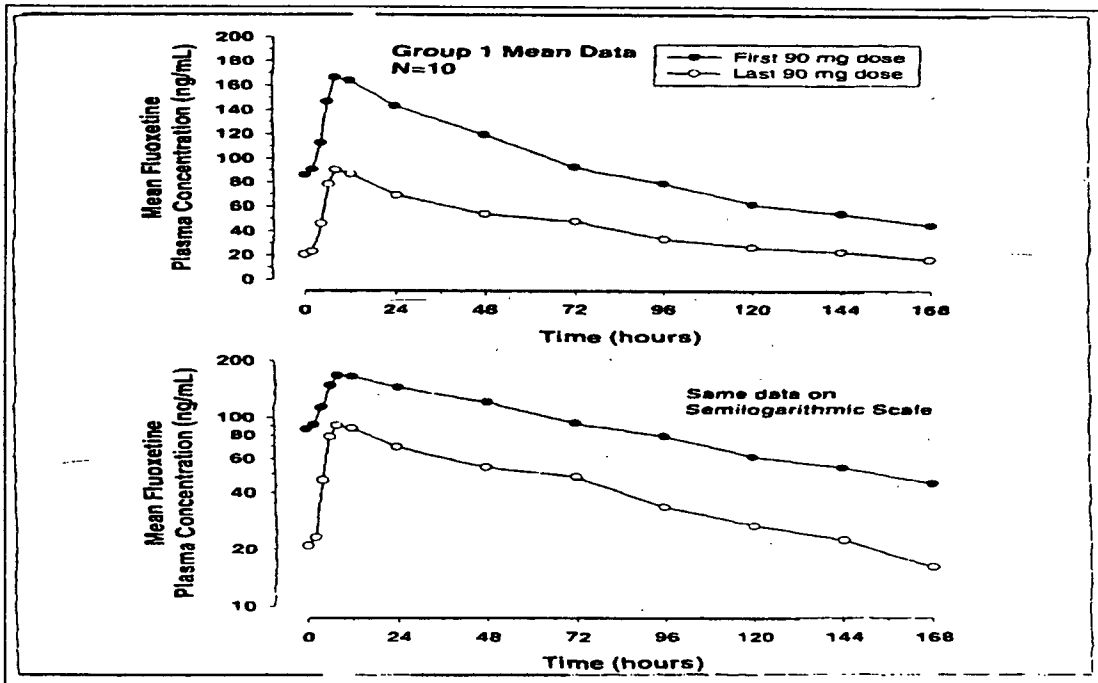


Figure HCJO.11.15. Mean fluoxetine plasma concentrations following the first 90 mg fluoxetine once-weekly dose (Days 22 to 29) and last 90 mg fluoxetine once-weekly dose (Days 57 to 64) for Group 1.

Figure 9

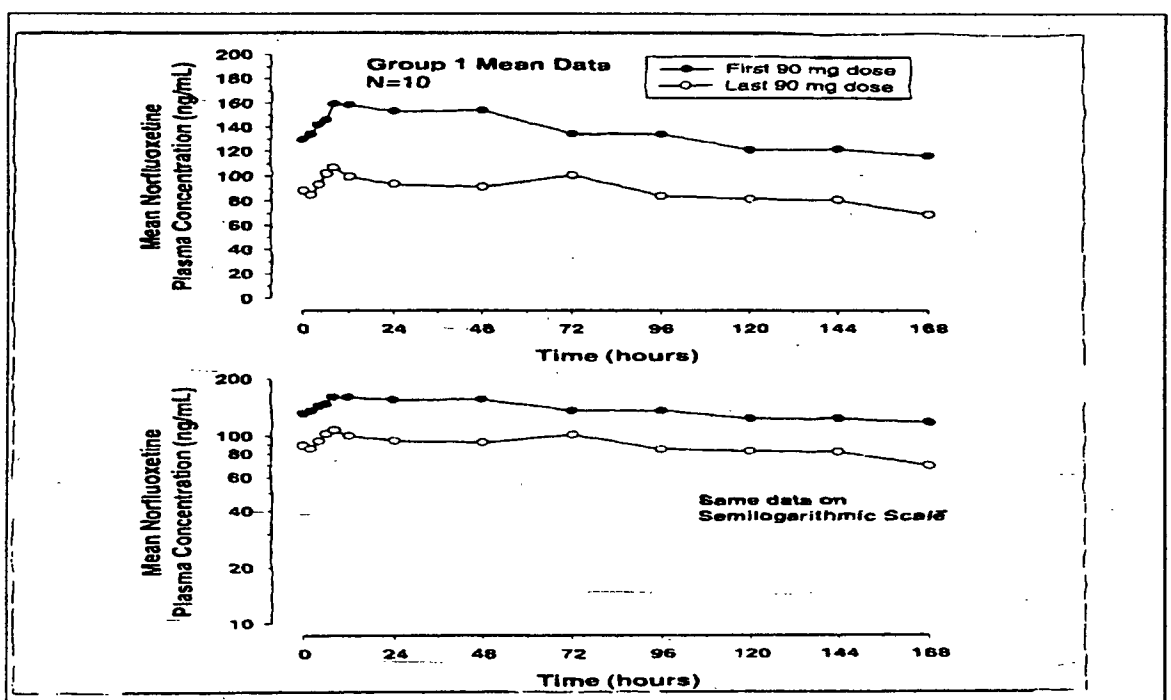


Figure HCJO.11.16. Mean norfluoxetine plasma concentrations following the first 90 mg fluoxetine once-weekly dose (Days 22 to 29) and last 90 mg fluoxetine once-weekly dose (Days 57 to 64) for Group 1.

Figure 10

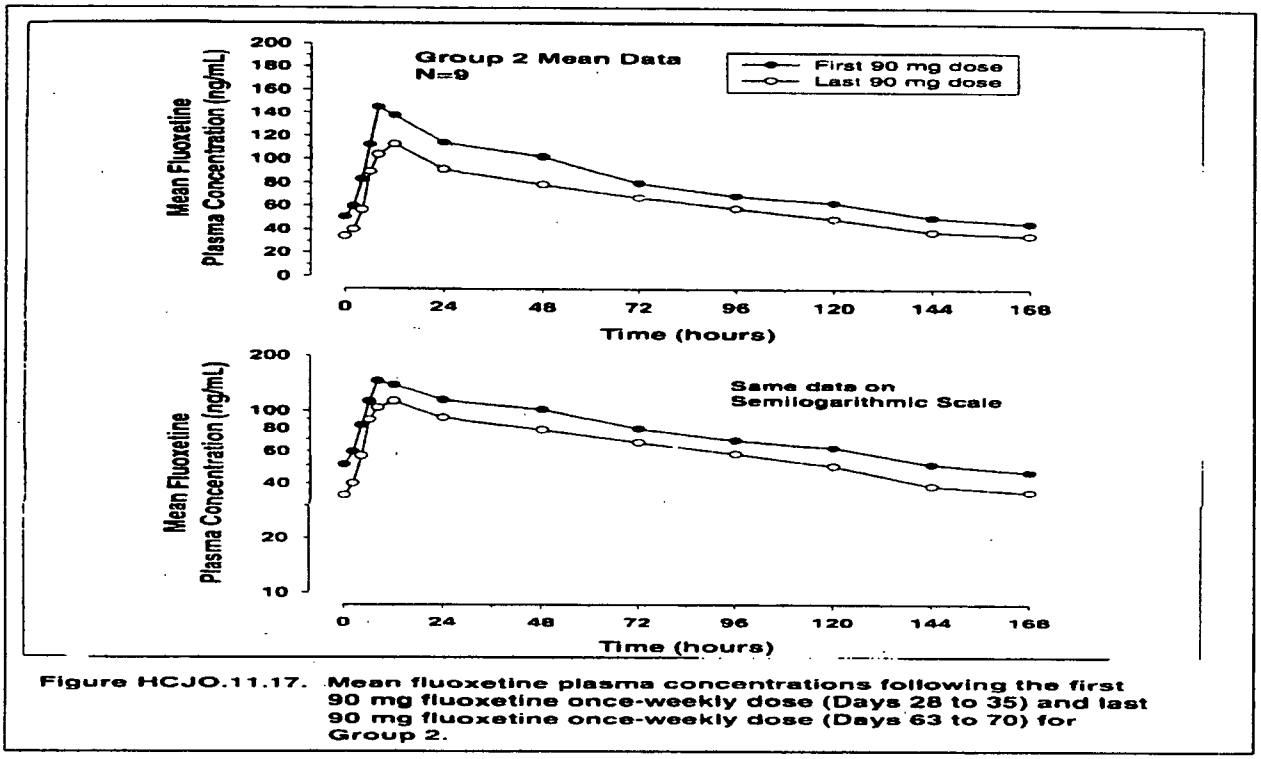


Figure HCJO.11.17. Mean fluoxetine plasma concentrations following the first 90 mg fluoxetine once-weekly dose (Days 28 to 35) and last 90 mg fluoxetine once-weekly dose (Days 63 to 70) for Group 2.

Figure 11

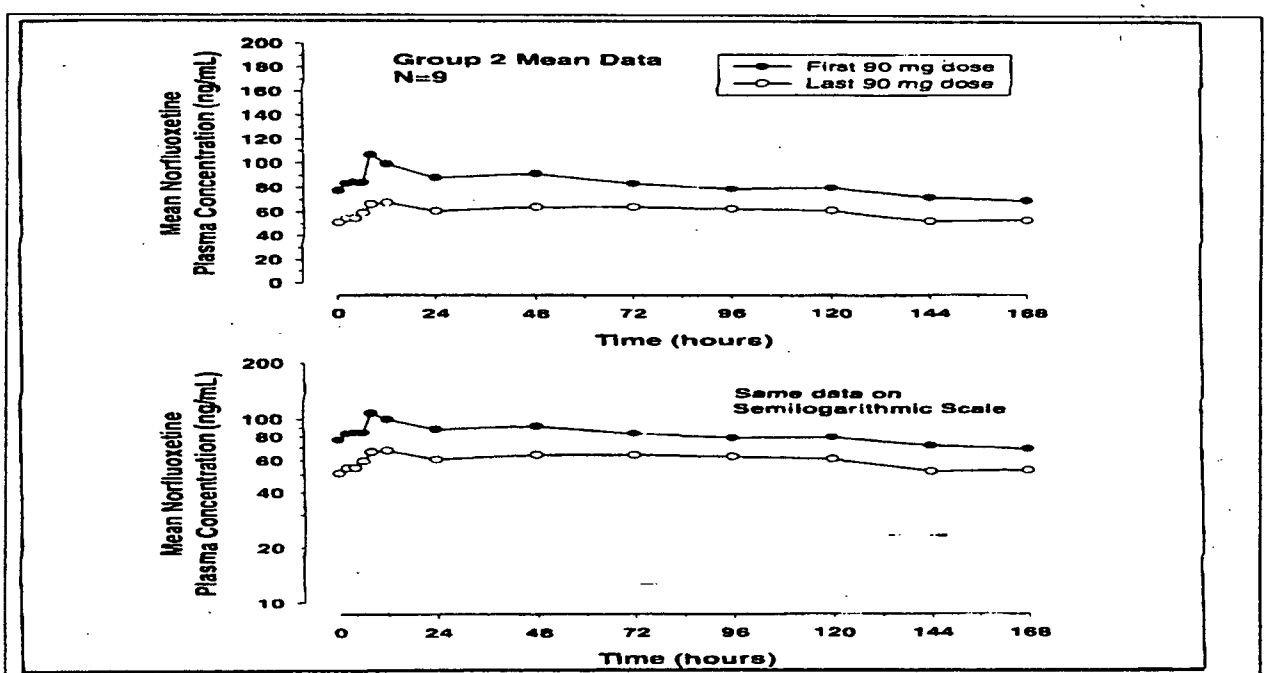


Figure HCJO.11.18. Mean norfluoxetine plasma concentrations following the first 90 mg fluoxetine once-weekly dose (Days 28 to 35) and last 90 mg fluoxetine once-weekly dose (Days 63 to 70) in Group 2.

Simulations of Noncompliance: The applicant has attempted to perform pharmacokinetic simulations using 2 different scenarios where there may be noncompliance to a prescribed regimen. Assumptions consistent with the application of linear pharmacokinetic principles were applied to a one compartment, first-order, oral absorption model. The model parameters were based upon a fitting of the mean plasma concentration data from participants of Group 1 in Study HCJO. Only fluoxetine plasma concentrations were considered in these simulation models.

The first scenario that was simulated was to establish the interval of time that fluoxetine concentrations do not differ by more (or less) than 20% between 2 doses (daily and weekly dosing). The simulations suggested that if individuals go off schedule by missing a daily or a weekly dose for a period of 24 hours, there will be a less than 20% change in fluoxetine concentration (see figure 12).

Figure 12

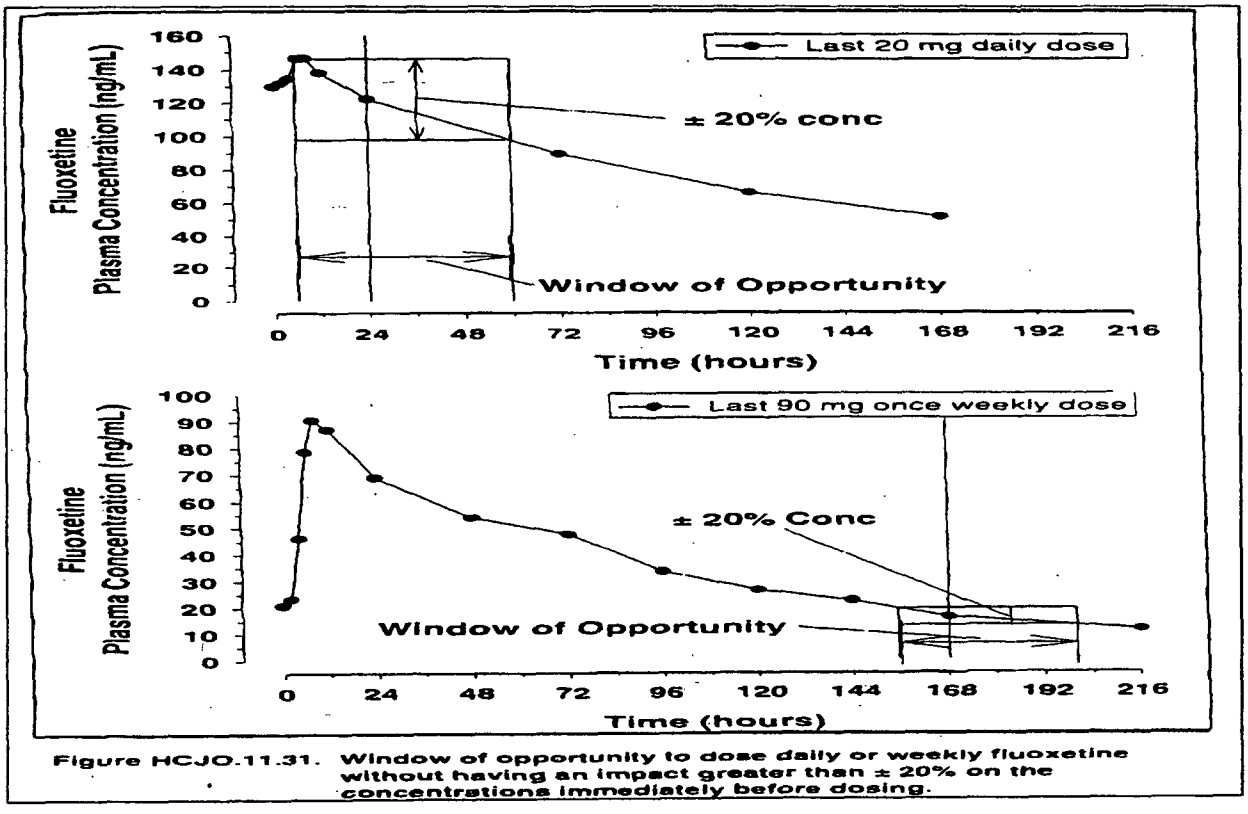


Figure HCJO-11.31. Window of opportunity to dose daily or weekly fluoxetine without having an impact greater than ± 20% on the concentrations immediately before dosing.

Simulations were also performed to assess the impact of missed doses on the pharmacokinetics of fluoxetine. The impact of 1) missing one daily 20 mg dose, 2) having the weekly dose delayed by 1 day and 3) having the weekly dose delayed by 5 days were compared. Figures 13-14 suggest that the impact of noncompliance is not significantly different for daily or weekly regimens. Missing a dose under the three conditions described above have only a minor impact on steady-state fluoxetine concentrations.

Figure 13

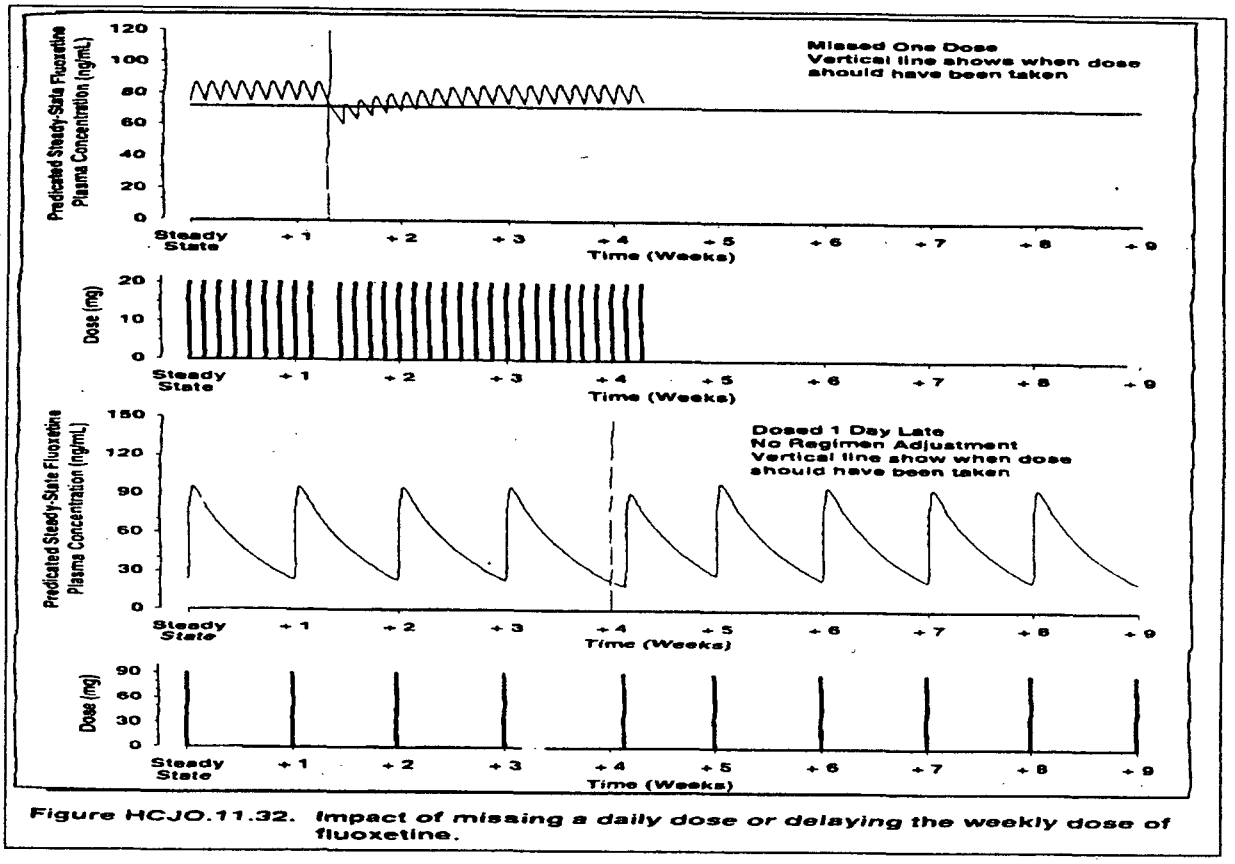


Figure HCJO.11.32. *Impact of missing a daily dose or delaying the weekly dose of* fluoxetine.

Figure 14

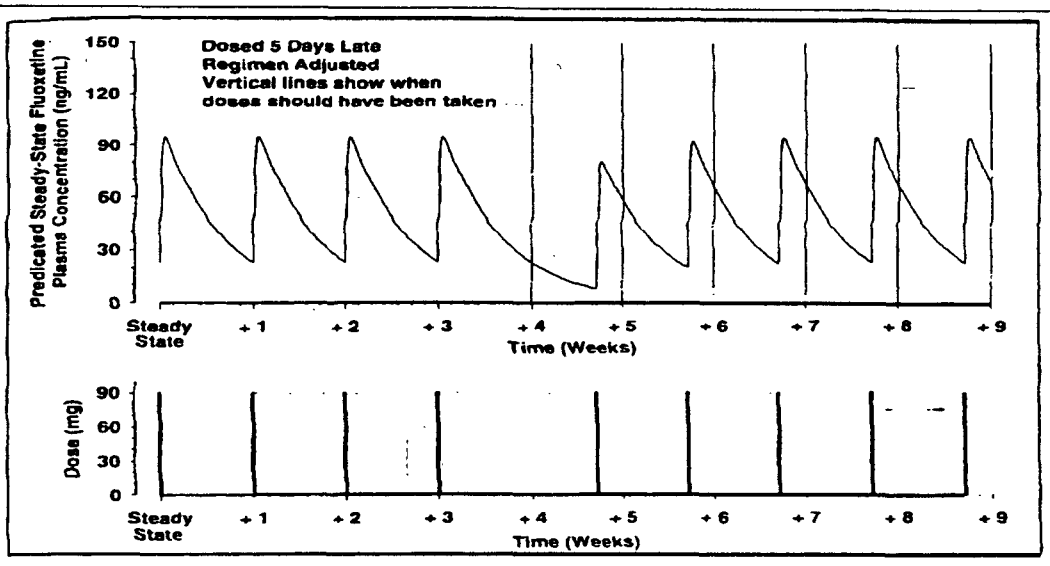


Figure HCJO.11.33. Impact of missing a weekly dose of fluoxetine for 5 days.

Conclusions:

1. The magnitude of the average steady state plasma concentration was in proportion to the total dose administered. Average steady state fluoxetine concentrations were approximately 50% lower following the once-weekly regimen compared to the once-daily regimen. The difference in average steady-state norfluoxetine concentrations between the 2 regimens was less pronounced.
2. Fluctuation between peak and trough concentrations were increased from daily to weekly dosing. (for fluoxetine: 24% (daily) to 164% (weekly) and for norfluoxetine: 17% (daily) to 43% (weekly)).
3. Comparison of once-daily and once-weekly dosing showed that peak fluoxetine concentrations were similar for both regimens at steady-state.
4. Fluoxetine and norfluoxetine steady state concentrations were maintained for the 7 days following the once-weekly treatment.
5. From a pharmacokinetic perspective, the transition from the 20 mg once-daily dosing to the 90 mg once-daily dosing ma be better achieved by giving the once-weekly dose 7 days after the last 20 mg dose.
6. Simulations of noncompliance for daily and weekly regimens showed that the impact of noncompliance is not significantly different for daily or weekly regimens. Missing a dose (for daily and weekly regimens) had minor impact on steady-state fluoxetine concentrations.

Title of study: Pharmacokinetic Analysis of Study BIY-MC-HCIZ: Weekly Enteric-Coated Fluoxetine Hydrochloride Versus Daily Fluoxetine or Placebo in the Continuation Treatment of Major Depression (Study HCIZ)

Objectives: The main objective of this efficacy study was to determine if the relapse rate for depressed patients given 90 mg enteric-coated fluoxetine once-weekly was similar to the relapse rate for patients given 20 mg fluoxetine daily, and lower than that for patients on placebo. A secondary objective was to assess the pharmacokinetics of fluoxetine in depressed patients during the various dosing regimens used in this study.

Study Design and Methods: The study was a double blind, randomized, parallel group study. Initially all patents (n=932) received 20 mg fluoxetine daily for 13 weeks (Period 2). (Period 1 = screening). A single blood sample was collected during four scheduled visits during this period for measurement of plasma fluoxetine and norfluoxetine. Of the 932 patients, 501 completed Period 2. These patients entered Period 3 in which 189 were randomized to continue on 20 mg once daily fluoxetine, 190 were switched to 90 mg once weekly and 122 were switched to placebo for 25 weeks. Plasma fluoxetine and norfluoxetine concentrations were measured during this period. Patients who relapsed were entered into an optional rescue phase of the study: those on 90 mg weekly were dose-escalated to 90 mg twice weekly, those on 20 mg once daily were increased to 40 mg once daily and the placebo patients were increased to 20 mg once daily. Plasma fluoxetine and norfluoxetine concentrations were also measured during the rescue phase in the relapsed patients.

Plasma samples were analyzed for fluoxetine and norfluoxetine using LC/MS/MS methods. The limit of quantification was ——. The method was linear n the range of —— The precision for QC samples (for fluoxetine) as expressed by %RSD ranged from —— and accuracy for QC samples (for fluoxetine) as expressed by %RE ranged from ——. The precision for QC samples (for norfluoxetine) as expressed by %RSD ranged from ——, and accuracy for QC samples (for norfluoxetine) as expressed by %RE ranged from ——.

Pharmacokinetic analysis utilized graphical/descriptive techniques to assess the fluoxetine dosing and concentration data. Comparisons between periods within a therapy group were made by Tukey's method adjusted for multiple comparisons.

Results:

Demographics: Of the 932 patients who entered the study, 501 were randomized to receive maintenance therapy of 20 mg once daily fluoxetine (189), 90 mg once weekly (190) or placebo (122). The mean age of these patients was 42 years (19-75 years), mean weight was 82 kg (43 to 168 kg). There were 342 females and 159 males. 449 patients were Caucasian and the remaining 52 were non-Caucasian. The treatment groups were similar in terms of the demographic characteristics.

Pharmacokinetics:

Pre-randomization Period (Period 2): All patients received 20 mg fluoxetine daily. During this Period, a single pharmacokinetic measurement was performed during 4 visits. Most patients receiving 20 mg daily fluoxetine achieved near steady state fluoxetine and norfluoxetine levels by approximately 3 weeks. Final steady state concentrations were achieved in most patients by 7 weeks. This is consistent with the half lives of fluoxetine (4-6 days) and norfluoxetine (4-16 days). There was a high inter individual variability in the pharmacokinetics of fluoxetine and norfluoxetine (Figure 1).

Figure 1

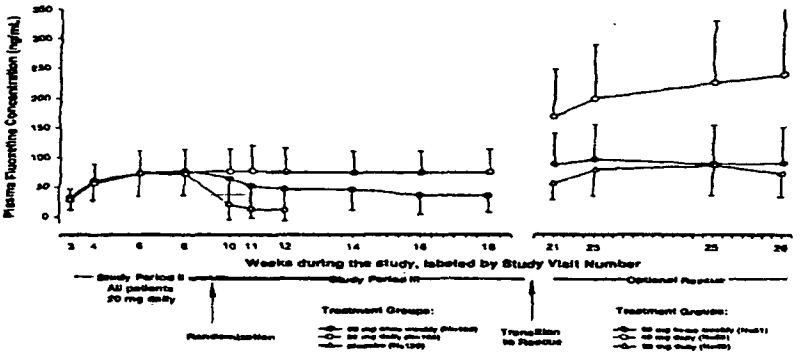
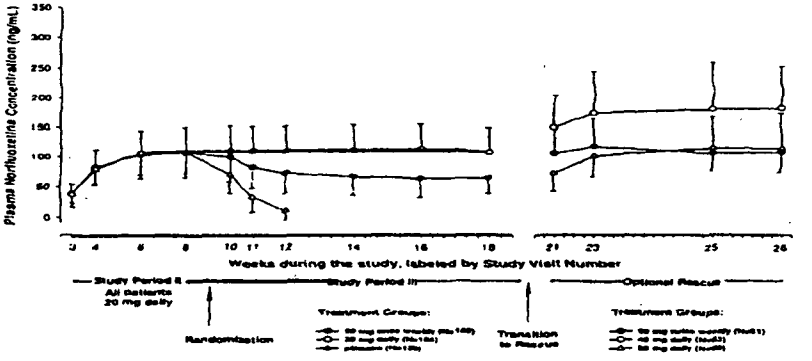


Figure A. **Mean (±SD) Plasma Fluoxetine Concentrations Over Study Visits**



X-axis is scaled for time in weeks (1 tick mark = 1 week) but is labeled by Study Visit Number
N=highest number of samples at a visit.

Figure B. **Mean (±SD) Plasma Norfluoxetine Concentrations Over Study Visits**

All 3 treatment groups had similar mean concentration-time profiles during Period 2. Average steady state fluoxetine concentrations were in the range of 71 to 75 ng/ml and 106 –107 ng/ml for norfluoxetine concentrations. Therefore, there were no baseline differences in the fluoxetine and norfluoxetine concentrations prior to randomization.

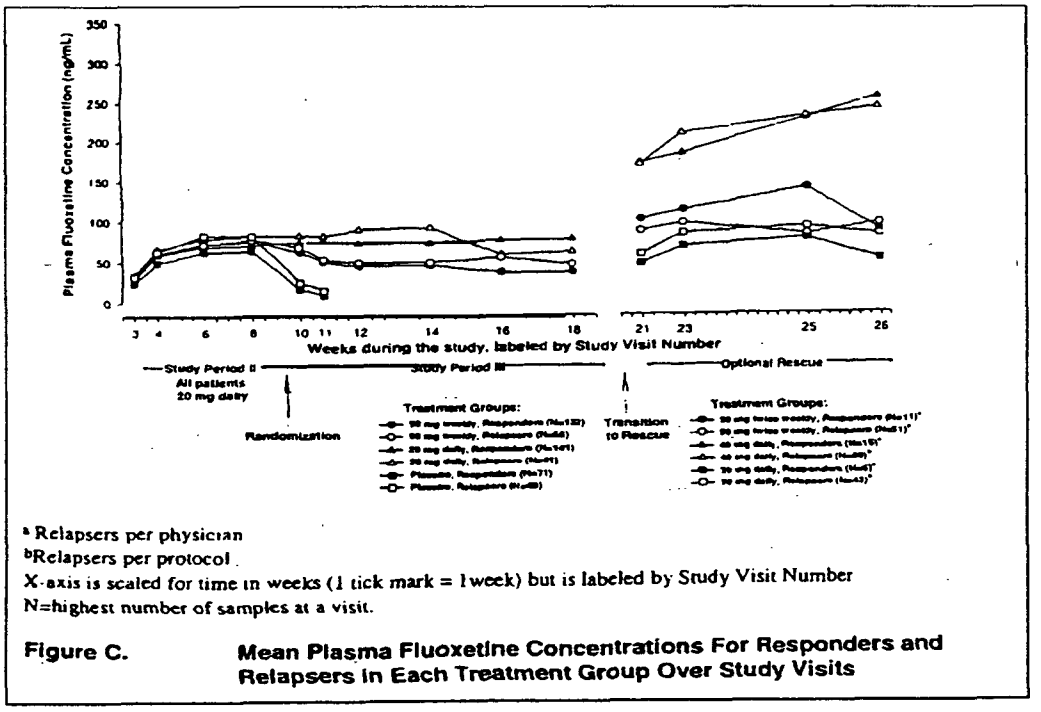
Post-randomization Phase (Period 3): Following randomization of patients to 90 mg once weekly, 20 mg once daily or placebo, there was a separation between the groups in terms of plasma fluoxetine and norfluoxetine concentrations (Figure 1). For patients on placebo, plasma fluoxetine concentrations fell to non-detectable limits approximately 7 weeks into the randomization phase. For patients randomized to 20 mg once daily, the mean fluoxetine and norfluoxetine concentrations remained at pre-randomization steady-state levels throughout the end of Period 3. For patients who were placed on 90 mg once weekly, fluoxetine and norfluoxetine concentrations fell from their pre-randomization levels and reached new steady-state concentrations by approximately 7 weeks into the randomization phase. The new steady-state fluoxetine and norfluoxetine concentrations were approximately 57% and 66% of the corresponding concentrations during Period 2. The reduced steady-state concentrations are in agreement with what has been observed in study HCJO (Multiple Dose, Fluoxetine Steady State Switch from Once Daily to Once Weekly Dosing). Also

90 mg once weekly dose is 64% of the total weekly dose of 20 mg once daily (90 mg/weekly vs. 140 mg/weekly).

Rescue Phase: Patients who relapsed during Period 3 were provided the option to enter the rescue phase of the study. Patients assigned to placebo returned to 20 mg once daily, these patients mean steady state fluoxetine concentrations returned to pre-randomization (Period 2) levels. Patients assigned to 20 mg once daily were switched to 40 mg once daily; these patients demonstrated an increase in the average steady-state concentrations of fluoxetine and norfluoxetine. Those patients that were assigned to 90 mg once weekly were switched to 90 mg twice weekly; these patients had a doubling in the average steady state concentrations of fluoxetine and norfluoxetine compared to 90 mg once weekly. However, these concentrations were slightly higher than concentrations observed during Period 2 at a dose of 20 mg once daily. (See Figure 1).

Relapsers versus Responders: Fluoxetine and norfluoxetine concentrations between responders and relapsers have been compared during Periods 2, 3 and the rescue phase. For each treatment group, the concentrations of fluoxetine and norfluoxetine between responders and relapsers were similar. This suggests that plasma fluoxetine/norfluoxetine concentrations are probably not predictable of the clinical response of whether patients will respond or relapse. See Figures 2 and 3.

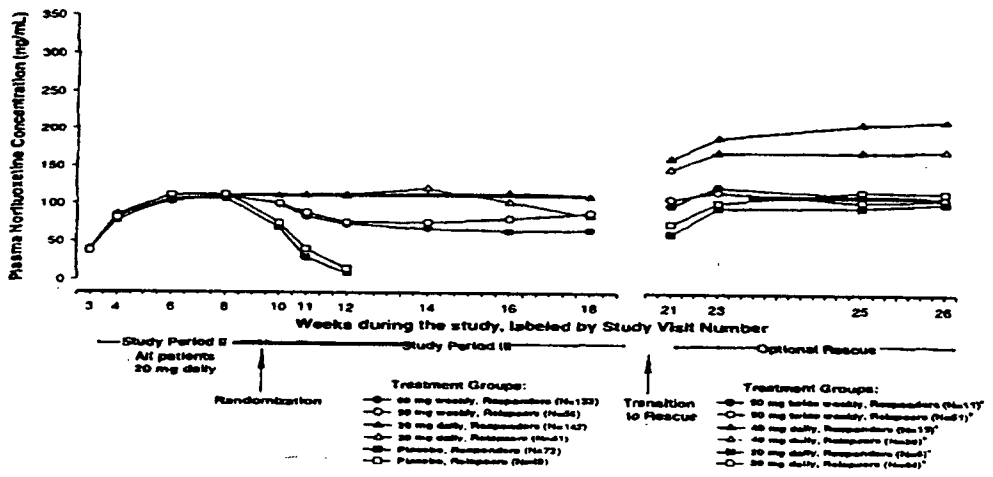
Figure 2



[a] Relapsers per physician
[b] Relapsers per protocol
X-axis is scaled for time in weeks (1 tick mark = 1 week) but is labeled by Study Visit Number
N=highest number of samples at a visit.

Figure C. **Mean Plasma Fluoxetine Concentrations For Responders and Relapsers in Each Treatment Group Over Study Visits**

Figure 3



[a] Relapsers per physician
[b] Relapsers per protocol
X-axis is scaled for time in weeks (1 tick mark = 1 week) but is labeled by Study Visit Number
N=highest number of samples at a visit.

Figure D. **Mean Plasma Norfluoxetine Concentrations For Responders and Relapsers in Each Treatment Group Over Study Visits**

Conclusions:

1. Mean steady state plasma fluoxetine and norfluoxetine concentrations for patients who received 90 mg once weekly were approximately 60% of the mean concentrations achieved following a dose of 20 mg once daily.
2. Mean steady state fluoxetine /norfluoxetine concentrations following 90 mg once weekly were similar in depressed patients in this study and in healthy volunteers from study HCJO. (Fluoxetine: healthy (53 ng/ml) versus patients (43 ng/m)l; Norfluoxetine: healthy (75 ng/ml) versus healthy (69 ng/ml)).
3. Plasma fluoxetine/norfluoxetine concentrations are probably not predictable of the clinical response of whether patients will respond or relapse.

Title of study: Pharmacokinetic Analysis of Study BIY-MC-HCJR: Weekly Enteric-Coated Fluoxetine Hydrochloride Versus Daily Fluoxetine or Placebo: Patient Adherance to a Dosing Regimen (Study HCJR)

Objectives: The main objective of this efficacy study was to determine if the level of adherance of patients given enteric-coated fluoxetine 90 mg once weekly was not significantly inferior to the adherance of patients given fluoxetine 20 mg once daily.

Study Design and Methods: The study was an open-label, randomized, parallel group study in 117 patients with major depression. All patients initially received fluoxetine 20 mg once daily for 4 weeks (Period 1). Electronic monitoring of when the fluoxetine bottle cap was removed and replaced was the primary measure of adherance to the prescribed dosing regimen. At the end of Period 1, a single blood sample was collected from each patient for measurement of steady state fluoxetine and norfluoxetine concentrations. At the start of Period 2 which lasted 12 weeks, 53 patients were randomized to continue receiving 20 mg once daily fluoxetine and 56 subjects were switched to 90 mg once weekly fluoxetine. At the end of Period 2, a single blood sample was collected from each patient for measurement of steady state fluoxetine and norfluoxetine concentrations. Steady state fluoxetine and norfluoxetine concentrations were used as secondary measures of adherance to the prescribed dosing regimen.

Plasma samples were analyzed for fluoxetine and norfluoxetine using LC/MS/MS methods. The limit of quantification was ——— The method was linear n the range of ———. The precision for QC samples (for fluoxetine) as expressed by %RSD ranged from ——— and accuracy for QC samples (for fluoxetine) as expressed by %RE ranged from ———. The precision for QC samples (for norfluoxetine) as expressed by %RSD ranged from ——— and accuracy for QC samples (for norfluoxetine) as expressed by %RE ranged from ———

Pharmacokinetic analysis utilized graphical/descriptive techniques to assess the fluoxetine dosing and concentration data. Data from patients randomized to the once weekly regimen was analyzed separately from patients in the once daily group. The analysis primarily focused on the within-patient comparison of plasma concentration data during Period 1 and Period 2. The ratios of plasma concentration values (Period 2 to Period 1) were used to categorize patients as compliant or noncompliant. The ratio of the weekly dose in Period 2 (90 mg or 140 mg) to the weekly dose in Period 1 (140 mg) was used to set the standard for the expected plasma concentrations ratios under compliant conditions. For the once weekly treatment, if patient was compliant the ratio should be 0.64 or 64%. A 20% window was allowed around the expected ratio. Therefore, acceptable ranges for compliance for once weekly were —— and —— for the once daily treatment.

Results:

Demographics: Of the 117 patients who entered the study, 53 patients were randomized to continue receiving 20 mg once daily fluoxetine and 56 subjects were switched to 90 mg once weekly fluoxetine. There were measurable fluoxetine and norfluoxetine concentrations during both study periods in 42 patients on the once weekly treatment and in 44 patients on the once daily regimen.

Patients ranged in age from 22 to 47 years (mean =46 years) and weighed between 50 to 108 kg (mean = 75 kg). There 69 females and 17 males, all of who were Caucasian.

Pharmacokinetics: Patients randomized to once weekly regimen (90 mg weekly dose) in Period 2 demonstrated a decrease in steady state fluoxetine and norfluoxetine concentrations from Period 1 (140 mg weekly dose). The average ratio of plasma concentrations (Period 2 to Period 1) was 61% for fluoxetine and 77% for norfluoxetine. Patients randomized to once daily regimen (140 mg weekly dose) in Period 2 demonstrated similar steady state fluoxetine and norfluoxetine concentrations from Period 1 (140 mg weekly

dose). The average ratio of plasma concentrations (Period 2 to Period 1) was 92% for fluoxetine and 96% for norfluoxetine

Patients on the 90 mg weekly regimen were classified as compliant if the plasma concentration ratio was between —— . Of the 42 patients randomized to the weekly regimen, 33 (79%) were classified as compliant based on this measure. Patients on the 20 mg daily regimen were classified as compliant if the plasma concentration ratio was between —— Of the 44 patients randomized to the weekly regimen, 37 (84%) were classified as compliant based on this measure Figures 1 and 2).

Figure 1

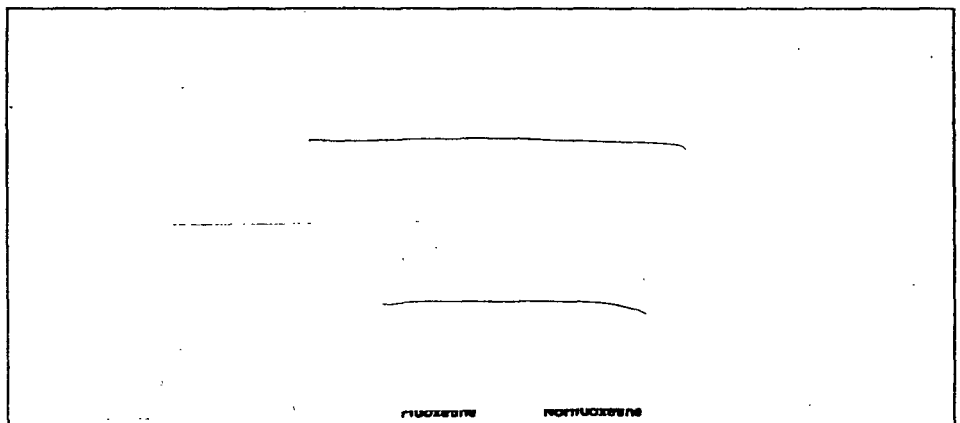
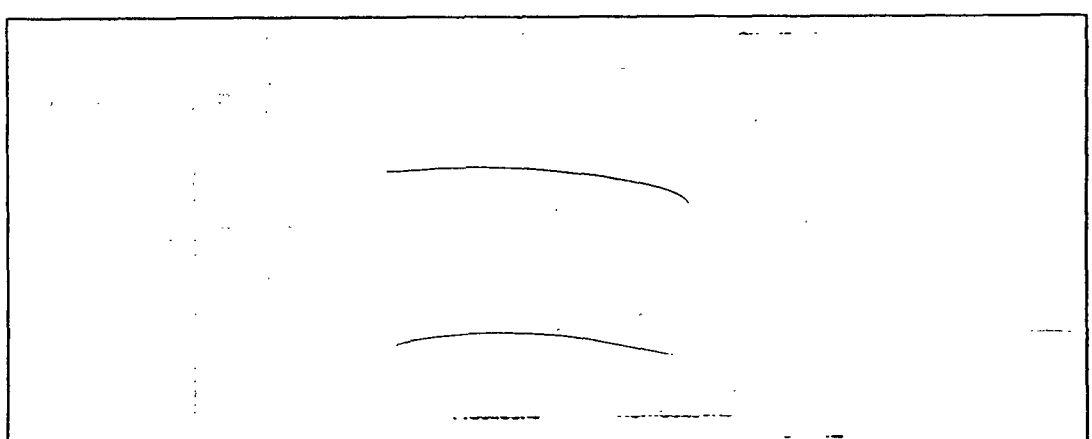


Figure C **Fluoxetine and Norfluoxetine Concentration Ratios for Patients in WEEKLY-90 Treatment Group Classified as Compliant or Noncompliant**

Figure 2



Note: Patient #8743 had a fluoxetine ratio of 1099% which is shown as 200% in this plot.

Figure D **Fluoxetine and Norfluoxetine Concentration Ratios for Patients in DAILY-20 Treatment Group Classified as Compliant or Noncompliant**

These ratios were compared to the results obtained from the primary compliance analysis determined from electronic cap monitoring. The mean adherance proportion from the primary analysis was 86% during the once weekly regimen and 79% during the once daily treatment. The results obtained from the two measures were comparable.

Conclusions:

1. The compliance rate (based on plasma fluoxetine and norfluoxetine concentrations) was —— for patients randomized to the 90 mg once weekly regimen and —— for patients randomized to the 20 mg once daily treatment. These differences are not significant.

Dissolution Testing for the enteric-coated pellet formulation of fluoxetine: Fluoxetine HCl is classified as a BCS Class 1 compound.

testing was carried out for 2 hours in 250 ml of 0.1N HCl followed by buffer stage testing in 250 ml of buffer at pH 6.8. The limit of no more than release in 2 hours in 0.1 N HCl is derived from the USP criteria for delayed release articles. The applicant has proposed a dissolution specification of Q = in minutes in pH 6.8 buffer (using USP apparatus 3) on the basis that this is supported by the stability data. Tables 1, 2 and 3 show mean (range) data for batches of fluoxetine extended release pellet formulation.

Table 1

Test	Regd. Stability Lot CTM00237	CTM00238	CTM00239	Proposed Specifications
(%)				See footnote 1.
(%)				See footnote 1.
(%)				See footnote 1.
Dissolution (%). Mean (Range) n = 12 2 hours, gastric	1 (0-1)	1 (0-1)	1 (1-1)	Conforms to requirements for drug release <724>. Q = at minutes in buffer stage.
	54	56	55	
	85	84	85	
	95	95	97	
	97	97	98	
water (%)	1.2	1.0	1.1	See footnote 2.

Table 2

Test	Regd. Stability Lot CTM00237	CTM00238	CTM00239	Proposed Specifications
(%)				See footnote 1.
(%)				See footnote 1.
(%)				See footnote 1.
Dissolution (%). Mean (Range) n = 12 2 hours, gastric				Conforms to requirements for drug release <724>. Q = at minutes in buffer stage.
water (%)				See footnote 2.

Table 3

Test	Clinical Trial Lot CT07218	CT08182	CT10800	CT11374
Largest Individual Related Substance (%): Other[1]	See footnote 2.	See footnote 2.	0.03	0.04
(%)	[redacted]			
(%)				
(%)				
Dissolution (%): Mean B04634 (B05287)[4] 2 hours, gastric	[redacted]			

The applicant was requested to submit individual dissolution data for the batches that were use din the pivotal bioequivalence study (see attached).

Recommendation: Based on the individual dissolution data for the batches used in the pivotal BE study, a dissolution specification of Q=[redacted] in 45 minutes may be recommended.

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2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable

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